5 days the product was suction filtered and recrystallized from acetonitrile to yield 3.51 g (81%) of **1b:** mp 172–173 °C dec; IR 3300 (OH), 3200, 3400 (NH_2), 1640 (amide I C=O), 744 (CH out-of-plane deformation) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.15; N, 14.43. Found: C, 55.85; H, 5.18; N, 14.30.

2,3:5,6-Dibenzo-1,7-dihydroxy-7a,8a-diaza-4-oxaoctahydro-*s*-indacen-8-one (2b). A stirred mixture of *o*-phthalaldehyde (3.15 g, 0.0235 mol), urea (0.67 g, 0.112 mol), and 100 mL of distilled water was treated with 5 mL of 2.5% aqueous NaOH; stirring was continued for 6 days. Recrystallization of the suction-filtered crystals from acetonitrile yielded 2.75 g (80%) of **2b:** mp 218–219 °C dec; IR 3333 (OH, v br), 1653 (amide I C=O), 720–780 (CH out-of-plane deformation)[8] cm^{-1}; mass spectrum *m/e* 310 (M), 309 (M − 1), 308 (M − 2), 307 (M − 3), aromatic cluster *m/e* 77, 78, 79.

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.81; H, 4.52; N, 9.03. Found: C, 65.92; H, 4.55; N, 8.97.

Monomethoxy, Monoethoxy, Dimethoxy, and Diethoxy Derivatives of 2a and 2b: 3a–d and 4a–d. All compounds were prepared by a modification of the method described in ref 1a. Urea or thiourea (0.015 mol), added to a solution of the sodium alkoxide (0.030 g at Na in 50 mL of the alcohol), was added dropwise over a period of 15 min to a rapidly stirred solution of *o*-phthalaldehyde (4.02 g, 0.030 mol) in 200 mL of the alcohol. In all cases, 24 h of stirring and standing for 2 weeks, a small amount of precipitate was evident. This was removed by suction filtration, and the filtrate was divided into two equal portions. One portion was immediately concentrated on a rotary evaporator. Resulting crystals were suction filtered, combined with the original precipitate, and recrystallized from acetonitrile. They were shown to be the monoalkoxy derivatives, **3a–d.** The second portion of filtrate was acidified with 6 N HCl until pHydrion paper showed a pH of ~1 when precipitation began. Dropwise addition of 6 N HCl was continued until reaction mixtures contained voluminous precipitates. Crystals were suction filtered, recrystallized from acetonitrile, and shown to be the dialkoxy derivatives **4a–d.** Further precipitation occurred for ~1 week. All derivatives gave positive Zeisel tests.

Yields (%) and melting points (dec): **3a,** 28, 180–182 °C; **3b,** 33, 205–206 °C; **3c,** 58, 192–193 °C; **3d,** 21, 218–219 °C; **4a,** 64, 173–174 °C; **4b,** 52, 227–228 °C; **4c,** 12, 179–180 °C; **4d,** 31, 229–230 °C. IR (cm^{-1}): OH 3400 (**3a**), 3440 3380 (**3c**), 3430 (**3d**); amide I C=O 1655 (**3b**), 1655 (**3d**), 1650 (**4b**), 1666 (**4d**); CH out-of-plane deformation 755 (**3a**), 754 (**3c**), 747 (**4a**), 750 (**4c**), see ref 8 for **3b, 3d, 4b,** and **4d.**

Anal. Calcd for $C_{18}H_{16}N_2O_3S$ (**3a**): C, 63.51; H, 4.74; N, 8.23, S, 9.42. Found: C, 63.40; H, 4.71; N, 8.24; S, 9.34. Calcd for $C_{18}H_{16}N_2O_4$ (**3b**): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.77; H, 5.06; N, 8.67. Calcd for $C_{19}H_{18}N_2O_3S$ (**3c**): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.44; H, 5.10; N, 7.82; S, 8.97. Calcd for $C_{19}H_{18}N_2O_4$ (**3d**): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.17; H, 5.36; N, 8.23. Calcd for $C_{19}H_{18}N_2O_3S$ (**4a**): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.27; H, 5.00; N, 7.97; S, 9.12. Calcd for $C_{19}H_{18}N_2O_4$ (**4b**): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.32; H, 5.30; N, 8.24. Calcd for $C_{21}H_{22}N_2O_3S$ (**4c**): C, 65.95; H, 5.80; N, 7.32; S, 8.32. Found: C, 65.77; H, 5.81; N, 7.29; S, 8.30. Calcd for $C_{21}H_{22}N_2O_4$ (**4d**): C, 68.86; H, 6,01; N, 7.65. Found: C, 68.55; H. 6.25; N, 7.56.

Conversion of Compounds of Structure 3 to Compounds of Structure 4. These conversions were accomplished as described for formation of compounds of structure **4** above. Yields varied from 51 to 85%.

Conversion of 2b to 4d. After stirring for 10 days, a mixture of 300 mL of 95% ethyl alcohol, 3 mL of 6 N HCl, and 0.62 g (0.002 mol) of **2b** remained heterogeneous. Heating to 70 °C resulted in homogeneity. Cooling, suction filtration, and washing with acetone and 95% ethyl alcohol yielded product (0.70 g, 96%) shown to be identical with **4d** by undepressed mixture melting point (229–230 °C) and identical IR spectrum.

Registry No.—*o*-Phthalaldehyde, 643-79-8; thiourea, 62-56-6; urea, 57-13-6.

References and Notes

(1) (a) R. D. Reynolds and R. J. Conboy, *J. Org. Chem.*, **30,** 2251 (1965); (b) R. D. Reynolds, D. F. Guanci, D. L. Arendsen, and R. F. Wickman, *ibid.*, **35,** 3940 (1970).

(2) It has been shown (ref 1b) that *N*-methylurea reacts with *o*-phthalaldehyde to form a monoadduct of the isoindoline type. Secondary amides (acetanilide, *N*-methylacetamide, *N*-methylformamide) did not react.

(3) It should further be noted that trans OH groups in the monoadducts would result in chirality. Many attempts to resolve these compounds failed.

(4) F. D. Chattaway and E. J. F. James, *J. Chem. Soc.*, 109 (1934); *Proc. R. Soc. London, Ser. A,* **137,** 481 (1932); *ibid.*, **134,** 372 (1931).

(5) Melting points were taken on a Büchi melting point apparatus previously calibrated against standard substances; IR spectra were determined on a Beckman IR 8 spectrophotometer in KBr pellets. A Varian A60 spectrometer was used for 60-MHz NMR spectra; 100-MHz spectra were run on a Varian HA-100 spectrometer. Mass spectra were determined on a Perkin-Elmer-Hitachi instrument, Model RUM-GE, at 60 °C. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or determined on a Perkin-Elmer 240 C, H, N analyzer. All stirring was magnetic, and all products isolated were white crystals.

(6) J. D. Bill and D. S. Tarbell *Org. Synth.*, **34,** 82 (1954).

(7) Many variations of this procedure were attempted. All resulted in mixtures of **1b** and **2b.** Recrystallization of **1b** must be carried out very carefully; otherwise, contamination by **2b** occurs.

(8) Six strong peaks occur in this spectral range. This pattern is typical of all compounds isolated as products from 2 mol of *o*-phthalaldehyde/mol of urea.

Catalytic Hydrogenation of Some Acylguanidines

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The behavior of several acylguanidines toward low-pressure hydrogenation over PtO_2 catalyst was investigated. Creatinine (**3**) and alacreatinine (**7a**) gave cleanly the corresponding cyclic guanidines, iminoimidazolidines **4** and **8a.** β-Alacreatinine (**9**) also could be hydrogenated in aqueous acid to iminohexahydropyrimidine **10,** but the same reaction in water gave a mixture of products. Only guanidine itself could be isolated from the hydrogenation of acetylguanidine, while the simple amide analogue pyrrolidinone was not reduced under these conditions and gave γ-aminobutyric acid under forcing conditions. The glycocyamides alacreatinine (**7a**) and phenylalacreatinine (**7b**) were prepared by acid-catalyzed cyclization of the corresponding optically active α-guanidino acids. In both cases, the resulting glycocyamidines were racemic. When the hydrogenation of creatinine was carried out in D_2O, the product 2-imino-1-methylimidazolidine (**23**) contained two deuterium atoms at C-4 and two at C-5, thus suggesting that hydrogenation would also lead to racemization of an α-chiral center.

If the preparation of alkylguanidines could be effected by reduction of the corresponding acylguanidines, the process would be of considerable utility since a variety of acylguanidines is readily available.[1,2] We have recently[3] developed a procedure using lithium aluminum hydride which accomplishes this conversion. In pursuit of perhaps an alternative and more convenient process, we have investigated the catalytic hydrogenation of acylguanidines. Such reductions of acylguanidines have not been reported. Although amides can be so reduced, the conditions necessary invariably involve high

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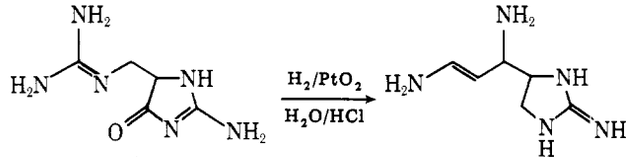


1 2

temperatures (>200 °C) and pressure (200–300 Torr).[4]

Our interest in the catalytic hydrogenation of acylguanidines was stimulated by the high yield conversion of the guanidinoglycocyamidine **1** to the cyclic guanidine **2**.[5] Was this a special case, influenced by the exo guanidine group proximal to the carbonyl, or did it reflect a general reaction? To answer this question, we examined a series of acylguanidines under hydrogenation conditions similar to those used in the preparation of **2** from **1**. We now report our catalytic reduction results.

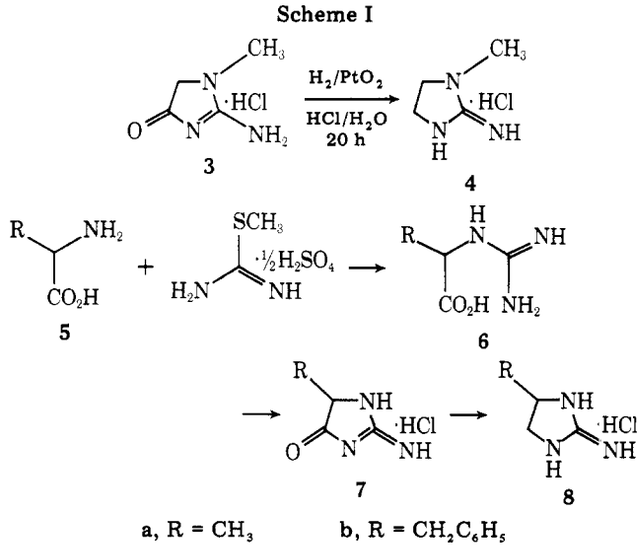
Because of its availability and similarity to the initial substrate **1**, creatinine hydrochloride (**3**) was chosen as the model compound to use in developing a set of standard hydrogenation conditions which were 0.05 M acylguanidine with 50 mol % of PtO_2 catalyst in a Parr shaker at a hydrogen pressure of 15–35 psi gauge. The reductions were monitored by withdrawing an aliquot for either NMR or UV analysis.

To our surprise, the ^1H NMR spectrum of the creatinine reaction mixture showed all the starting material to be consumed in less than 20 h of shaking at room temperature in 1.0 N HCl. ^{13}C and ^1H NMR analysis of the crude product obtained after filtration and evaporation indicated that the reduction gave cleanly the corresponding cyclic guanidine **4** in greater than 90% yield. Hydrogenations in either 0.1 N HCl or water did not make a significant difference in the rate of hydrogenation, yield, or purity of the cyclic guanidine product.

Alacreatinine hydrochloride (**7a**), a compound more directly analogous to **1**, was tried next. In contrast to creatinine, the rate of hydrogenation of alacreatinine under the above standard conditions was very slow (8 days). Cyclic guanidine **8a** was obtained, however, in good yield (Scheme I). The addition of varying amounts of acid to the solvent or the application of heat did not make consistent differences in the rate or yield. We attribute the lesser activity of alacreatnine (**7a**) to steric hindrance of its carbonyl group caused by the adjacent methyl. This added steric bulk might be a causative factor in the relatively slower hydrogenation of **7a**, although we did not anticipate a rate difference of such magnitude.

In order to explore the question of generality, two further acylguanidines were synthesized and subjected to the standard hydrogenation conditions. β-Alacreatinine hydrochloride (**9**)[2,6] was chosen as representative of the six-membered cyclic guanidine system, and acetylguanidine hydrochloride (**18**)[1] represented the open-chained series.

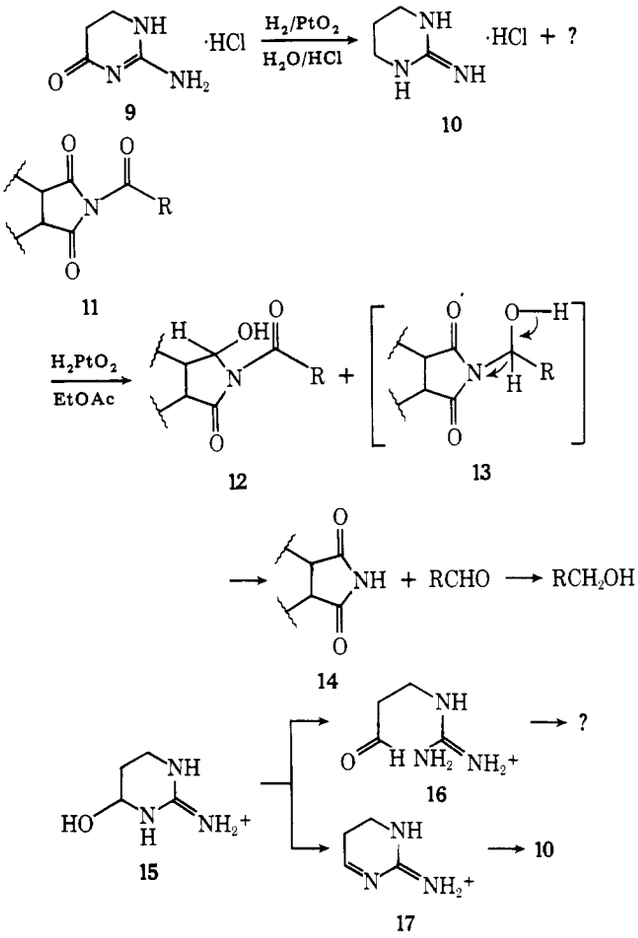
Scheme I



3 4 5 6 7 8

a, R = CH_3 b, R = $CH_2C_6H_5$

Scheme II

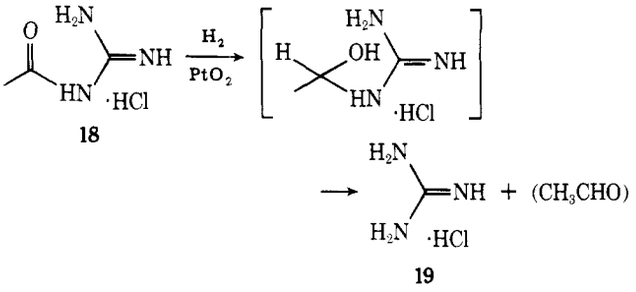


9 10 11 12 13 14 15 16 17

β-Alacreatine (**9**) was hydrogenated readily in water but gave, unexpectedly, a mixture of compounds as ascertained by NMR. Ion-exchange chromatography was utilized to separate the components, and with the strongly acid AG-50 resin and HCl as the eluent it was possible to recover the desired pure cyclic guanidine **10**. However, no other single component could be isolated, and TLC using a Weber visualizing spray[7] suggested that the product distribution was quite complex.

Although no literature precedent is available regarding the hydrogenation of acylguanidines, there is one report[8] that deals with the hydrogenation of the remotely related *N*-acylimide system. Hydrogenation of several different *N*-acylimides **11** over PtO_2 in ethyl acetate usually led to mixtures of the intact reduced hydroxylactam **12** and the parent imide **14**. Reduction presumably occurred by the same mechanism to carbinolimines **12** and **13**. In the latter case the intermediate exo carbinolimine **13** apparently fragmented in the manner indicated to give back the parent imide **14** and an aldehyde which was further reduced to an alcohol.

In the β-alacreatinine system, we thought that if the undesired side products were due to a similar fragmentation occurring from **15** to **16** in a mildly acidic milieu (the hydrochloride in water), increasing the acidity might protonate the hydroxyl group and promote the elimination of water to intermediate **17** instead of ring opening to the aldehydo guanidine **16** which then goes on to other products. It was found that addition of HCl to the reaction mixture did permit the clean hydrogenation of **9** to **10**. In 1 N HCl the hydrogenation was mostly over in 1 day and totally completed in 2 days, giving pure product in high yield as shown in Scheme II.



18

19

Acetylguanidine hydrochloride (**18**) failed to give any trace of the desired ethylguanidine under any of a variety of conditions, and only guanidine hydrochloride itself (**19**) could be isolated. The hydrogenation was carried out in both water and acid (0.1 and 1.0 N HCl). In water all starting material was consumed in less than 2 days at room temperature, and a quantitative yield of guanidine hydrochloride was isolated. A control experiment showed that **18** was stable in water for that period of time. Thus hydrogenation under these conditions probably proceeded to the intermediate carbinolguanidine stage. Fragmentation then gave guanidine hydrochloride (**19**) and acetaldehyde which was further reduced.

No reaction could be detected in any of the acid hydrogenations of acetylguanidine at room temperature for up to 40 h, but heating the reaction in 1 N HCl at 60 °C gave guanidine. This latter reaction was probably due in part, if not wholly, to hydrolysis since control studies indicated that **18** was hydrolyzed in 1 N HCl/60 °C at about the same rate as guanidine appeared in the hydrogenation reaction. The HCl salt was also hydrogenated in anhydrous glacial acetic acid that was 1 N in HCl, but no reaction occurred, even upon heating, as was also observed in the absence of added HCl. Attempted hydrogenation of acetylguanidine free base in water failed also. No reaction occurred at room temperature and only unidentified products were obtained upon heating.

In order to test the uniqueness of the acylguanidine hydrogenation and to conclusively rule out the possibility that a lactam might similarly be reduced under our conditions, we subjected 2-pyrrolidinone (**20**) to hydrogenation in 1 N HCl under the standard conditions. As expected, no reaction was observed at room temperature, and heating at 60 °C gave only the ring-opened γ-aminobutyric acid (**21**).

We can therefore summarize the relevant features of the above acylguanidine hydrogenation reactions. Five- and six-membered cyclic acylguanidines comprise a class of amides that are unique in that low-pressure catalytic hydrogenation reduces their carbonyl group to the level of methylene. The simple amide analogue pyrrolidinone failed to be hydrogenated under these conditions. The six-membered β-alacreatinine gave clean reduction only if acid was added, perhaps due to the fact that in water a competing fragmentation of an intermediate carbinolguanidine is operative. The simple open-chain acetylguanidine gave guanidine, probably through a carbinolguanidine intermediate, or no reaction. Also under forcing conditions in aqueous acid, guanidine was formed, but in the latter instance it is uncertain whether any reduction–fragmentation was involved or if only hydrolysis was responsible.

It is interesting to speculate why certain acylguanidines can be so easily hydrogenated while amides can not. Also, some cyclic carboxylic acid anhydrides can be hydrogenated over PtO_2 at room temperature and atmospheric pressure to the corresponding hemiacylal or lactone whereas simple esters are not reduced under these conditions.[9] The latter behavior was rationalized by proposing that the electron density at the carbonyl of anhydrides is less than that at ester carbonyls because the electron donation of the central anhydride oxygen must be shared by two carbonyls. This postulated dependence of reducibility on electron scarcity is also supported by the previously noted observation that although simple imides are not easily reduced, *N*-acylimides are so reduced.[8]

Our observations are consistent with this scheme. One would expect decreased amide resonance by donation of the nitrogen electron pair to the carbonyl in an acylguanidinium salt because this electron pair is already involved in the protonated guanidinium system. Also, the presence of this positively charged system so close to the carbonyl would tend to inductively decrease the electron density of the latter. It then becomes reasonable that the acylguanidine carbonyl should behave more like a ketone than an amide in its susceptibility to catalytic hydrogenation.

A potentially useful application of acylguanidine hydrogenation reaction would be the preparation of optically active cyclic guanidines of type **8**. Previously such compounds have been made in the *dl* form from the corresponding optically inactive diamines and an electrophilic reagent that provides the ring-forming one-carbon unit.[10] Or perhaps the optically active cyclic guanidine obtained by hydrogenation could be hydrolyzed to give an optically active diamine, which would otherwise be difficult to prepare without going through a resolution. The best starting materials for this process are, of course, the naturally occurring, optically active amino acids. The route involves reactions that have been well worked out for a number of systems, i.e., amidination of the amino acid and cyclization of the resulting α-guanidino acid to the glycocyamidine.

L-Phenylalanine (**5b**) was chosen initially as the optically active test substrate. The α-guanidino acid **6b** was prepared by standard procedures[11] and had $[\alpha]^{25}_{D}$ +42°. Cyclization to the glycocyamidine **7b** was performed in boiling, concentrated HCl, but to our surprise this latter compound was optically inactive. The simpler L-alanine system was also tried. L-Amidinoalanine (**6a**) was prepared and found to have $[\alpha]^{25}_{D}$ +10°. Cyclization with concentrated HCl gave **7a** as before but, again, the glycocyamidine was racemic.

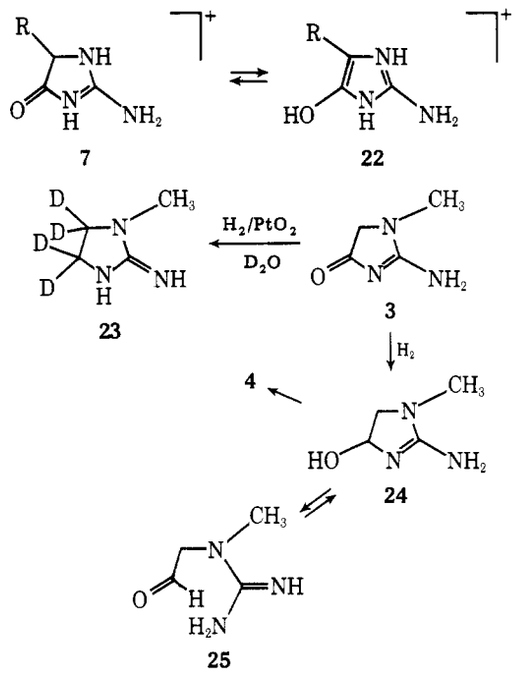
This racemization during cyclization of the α-guanidino acid to the glycocyamidine in hot, concentrated HCl was unexpected. It is known, of course, that peptides, when subjected to similar treatment, give optically active amino acids. No pertinent studies on optically active glycocyamidines have been reported and no optical activity data on these compounds have appeared. Some insight was gained in a study of exchange in D_2O. All the glycocyamidines **3, 7a, 7b** showed no deuterium incorporation at room temperature under mildly acid conditions; however, they did exchange under the more drastic conditions of the cyclization.

This exchange and racemization behavior can be explained by assuming the enolization equilibrium **7** ⇌ **22** (Scheme III). Again, the guanidinium resonance stabilization can be invoked to rationalize decreased amide-type delocalization and thus facilitate enolization.

On the assumption that milder, nonracemizing cyclization conditions could be found, we still wished to explore the hydrogenation reaction as a possible path to chiral alkylguanidines and diamines. Since the hydrogenation is conducted under conditions where the glycocyamidines do not exchange, retention of any starting chirality might be feasible. To ascertain any potential racemization, we attempted to replace the carbonyl oxygen with deuterium and conduct the reaction in D_2O. Thus by carrying out the reduction in $D_2O/Pt/H_2$ we also would take advantage of the frequently overlooked, rapid equilibration between D_2O and H_2 in the presence of platinum catalyst to form H_2O and D_2. Any racemization potential under these conditions would be detected by deuterium introduction at C-5.

To test this approach we hydrogenated creatinine (**3**) in D_2O and obtained in good yield a single crystalline product.

Scheme III



^{1}H NMR analysis of the product showed that essentially only one major absorption was present, the δ 2.9 peak assigned to the N-CH_3. There was a small absorption at δ 3.7 but this accounted for less than 10% of the total integration. Thus both of the product methylenes had fully incorporated deuterium to give the tetradeuterio derivative **23.** This assignment was confirmed by the mass spectrum which showed an M^+ -- HCl peak at *m/e* 103 and no appreciable $M^+ - HCl$ peak at *m/e* 99, the latter peak being exhibited by the protio compound. The $M^+ - HCl$ peaks are the most intense in both the deuterio and protio products.

It is clear from this experiment that complete exchange at the α position (C-5) took place rapidly during the hydrogenation reaction. We can postulate that this exchange proceeded through a ring-opened intermediate such as **25** which would rapidly incorporate deuterium via its enolization equilibrium and then be reduced to imidazolidine **4.** The possibility that the starting creatinine underwent exchange under the hydrogenation conditions but without hydrogenation was eliminated by a direct control experiment in which unchanged starting material was recovered. Thus this hydrogenation reaction, while a good method preparing cyclic guanidines, does not show promise as a method for synthesizing chiral compounds.

Experimental Section[12]

DL-*N*-Amidinoalanine (6a). DL-Alanine (**5a,** 4.46 g, 50 mmol) was dissolved in 1 N NaOH (50 mL, 50 mmol). To this was added *S*-methylisothiourea sulfate (6.95 g, 25 mmol), and the resulting solution was heated at 50 °C for 6 h. The water was evaporated at <70 °C, leaving a white crystalline mass which was dissolved in 30 mL of boiling water and allowed to cool to room temperature. Seeding with a pinch of the original residue gave the product as white stocky needles; recrystallization from water gave 1.5 g (23%) of **6a:** mp 218 °C dec; ^{1}H NMR δ 4.0 (q, 1 H), 1.3 (d, 3 H).

L-*N*-Amidinoalanine (6a). L-Alanine (**5a,** 4.46 g, 50 mmol) was treated with NaOH and *S*-methylisothiourea sulfate for 6 h as described above. After evaporation of the water the crude solid residue was recrystallized from water to give 3.37 g (52%) of **6a:** mp 215–216 °C (lit. mp[13] 247 °C); $[\alpha]^{25}_D$ +9.6° (*c* 1.04, H_2O). Anal. Calcd for $C_4H_9O_2N_3$: C, 36.6; H, 6.9; N, 32.0. Found: C, 36.3; H, 7.1; N, 31.8.

L-*N*-Amidinophenylalanine (6b). L-Phenylalanine (**5b,** 16.62 g, 100 mmol) was treated with 1 N NaOH (100 mL, 100 mmol) and *S*-methylisothiourea sulfate (13.93 g, 50 mmol) for 2 h as described above. The residue remaining after evaporation of the water was recrystallized two times from water to give 1.89 g (9%) of product as white needles: mp 241–242 °C (lit. mp[13] for DL compound, 240–242 °C); $[\alpha]^{25}_D$ +42.4 ° (*c* 1.98, 1 N NaOH). Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.3; N, 20.3. Found: C, 58.0; H, 6.4; N, 20.3.

DL-Alacreatinine Hydrochloride (7a). DL-*N*-Amidinoalanine (DL-**6a,** 1.1 g, 8.5 mmol) was refluxed for 3 h in concentrated HCl (25 mL). Evaporation of the solvent gave a white crystalline solid that was recrystallized from ethanol to give 900 mg (72%) of DL-**7a:** mp 203–204 °C (lit. mp[11] 203–204 °C); ^{1}H NMR δ 4.5 (q, 1 H), 1.5 (d, 1 H); ^{13}C NMR δ 177.3 (s), 157.1 (s), 55.5 (d), 15.4 (q).

The same result was obtained when L-*N*-amidinoalanine (L-**6a,** 2.0 g, 15.3 mmol) was refluxed with concentrated HCl (40 mL) for 3 h. The product had $[\alpha]^{25}_D$ 0° (*c* 2, H_2O).

DL-Phenylalacreatinine (2-Amino-5-phenylmethyl-4-oxo-4,5-dihydroimidazole) Hydrochloride (7b). L-*N*-Amidinophenylalanine (**6b,** 2.37 g, 11.5 mmol) was refluxed in concentrated HCl (40 mL) for 1 h. Evaporation of the solvent and recrystallization of the residue from isopropyl alcohol–ether gave 2.35 g (90%) of **7b** as flaky white crystals: mp 187–190 °C; $[\alpha]^{25}_D$ 0° (*c* 2.14, H_2O); ^{1}H NMR δ 7.6 (s, 5 H), 4.9 (m), 3.3 (d, 2 H).

Anal. Calcd for $C_{10}H_{12}N_3OCl$: C, 53.2; H, 5.4; N, 18.6. Found: C, 53.4; H, 5.4; N, 18.7.

β-Alacreatinine Hydrochloride (9). β-Alanine (8.91 g, 100 mmol) was treated with 1 N NaOH (100 mL, 100 mmol) and *S*-methylisothiourea sulfate (13.93 g, 50 mmol) for 1 h as described above. The crude *N*-amidino-β-alanine so obtained was recrystallized from water and immediately cyclized by boiling in concentrated HCl for 1 h. Evaporation and recrystallization from methanol gave 3.77 g (25% from β-alanine) of **9:** mp 265–269 °C (lit.[6] mp 268–271 °C); ^{13}C NMR δ 170.5 (s), 153.9 (s), 36.3 (t), 29.3 (t).

Acetylguanidine (18). This compound as the free base was prepared as previously reported:[1] mp 186–187 °C (lit. mp[1] 188–190 °C); ^{1}H NMR δ 2.0 (s); ^{13}C NMR 185.0 (s), 161.9 (s), 26.1 (q).

The hydrochloride salt was prepared by dissolving a portion of the free base in 1 N HCl and evaporating to dryness. The crude salt was recrystallized from ethanol–ether to give fine white needles: mp 142–144 °C; ^{13}C NMR δ 174.3 (s), 154.0 (s), 24.0 (q).

2-Imino-1-methylimidazolidine Hydrochloride (4). Creatinine hydrochloride (373 mg, 2.5 mmol), PtO_2 (88%, 342 mg, 1.25 mmol), and water (50 mL) were shaken in a Parr apparatus under 20–35 psi of hydrogen for 20 h. After filtration of the catalyst and evaporation of the solvent, 320 mg (94.5%) of **4** was obtained: ^{1}H NMR δ 3.65 (m, 4 H), 2.95 (s, 3 H); ^{13}C NMR δ 158.8 (s), 49.8 (t), 40.7 (t), 31.1 (q); MS *m/e* 99 ($M^+ - HCl$).

The picrate was formed in H_2O–ethanol from the hydrochloride: mp 195–196 °C (lit.[14] mp 194.5–195 °C).

2-Imino-4-methylimidazolidine Hydrochloride (8a). Alacreatinine hydrochloride (**7a,** 128 mg, 0.86 mmol), PtO_2 (121 mg, 0.43 mmol), and water (50 mL) were shaken with hydrogen as described above. The course of the reaction was followed by UV, monitoring the intensity of the acylguanidine absorption at 225 nm. After 8 days the 225-nm absorption had disappeared, and filtration and evaporation gave 106 mg (92%) of crystalline **8a:** ^{1}H NMR δ 4.4–3.2 (m, 3 H), 1.35 (d, 3 H); ^{13}C NMR δ 158.9 (s), 51.2 (d), 49.5 (t), 19.7 (q).

A picrate was prepared in water from the hydrochloride: mp 195–196 °C (lit.[15] mp 195–196 °C).

2-Iminohexahydropyrimidine Hydrochloride (10). A mixture of β-alacreatinine hydrochloride (**9,** 373 mg, 2.5 mmol), PtO_2 (342 mg, 1.25 mmol), and 1 N HCl (50 mL) were hydrogenated for 20 h as before. After filtration and evaporation, 305 mg (91%) of crystalline **10** were obtained: mp 150–153 °C (lit.[3] mp 153 °C); ^{1}H NMR δ 3.4 (t, 4 H), 2.1 (pentet, 2 H); ^{13}C NMR δ 153.6 (s), 38.0 (t), 19.2 (t).

A picrate was prepared from water from the hydrochloride: mp 184–187 °C (lit.[15] mp 185–186 °C).

Hydrogenation of β-Alacreatinine Hydrochloride (9) in Water. β-Alacreatinine hydrochloride (**9,** 373 mg, 2.5 mmol) and PtO_2 (342 mg, 1.25 mmol) were shaken with hydrogen as above in water (50 mL) for 19 h. Filtration and evaporation of the solvent gave a clear oil that slowly solidified. The ^{1}H NMR spectrum suggested the presence of more than one component: δ 5.5 (t, rel area 1), 3.7 (m, 8), 2.3 (m, 4.5). The crude product was chromatographed on a column of Bio-Rad AG 50-X8, −400 mesh resin (50 mL bed volume, 2 N HCl eluate). The elution was followed by TLC (silica gel, phenol saturated with water, visible with Weber spray)[7] and by this criterion **10** appeared as a deep-purple spot and could be isolated pure from the appropriate eluate fractions. The remaining fractions all contained a number of Weber-pink or red spots, and no other single compound could be isolated.

Hydrogenation of Acetylguanidine Hydrochloride (18). Acetylguanidine (**18,** 294 mg, 2.1 mmol), as the hydrochloride, and PtO_2 (342 mg) were shaken with hydrogen in water (50 mL) as before. The reaction was monitored by UV and stopped after 48 h when the

absorption at 227 nm had disappeared. Filtration and evaporation gave 203 mg (100% yield) of a white crystalline solid that proved to be identical with guanidine hydrochloride by TLC and ^{13}C NMR (δ 157.8).

When the hydrogenation was conducted in 1 N HCl no reaction was observed after shaking for 21 h at room temperature. The reaction mixture was then heated at 60 °C for 43 h at which point the UV absorption had disappeared. Filtration and evaporation of the solvent gave only guanidine hydrochloride. A duplicate reaction using 0.1 N HCl gave similar results.

Hydrogenation of Creatinine Hydrochloride (3) in D_2O. [4,5-$^2H_4$]-2-Imino-1-methyl-imidazolidine Hydrochloride (23). Creatinine hydrochloride (**3**, 373 mg, 2.5 mmol) was placed in an hydrogenation bottle and exchanged four times with D_2O by dissolution and evaporation. To this was then added PtO_2 (342 mg, 1.25 mmol) and D_2O (50 mL, 99.8% d), and the resultant mixture was hydrogenated as before for 26 h. After filtration and evaporation, 319 mg (89%) of a white crystalline solid was obtained: ^1H NMR δ 2.95 (s). The product was exchanged several times with water as before: MS *m/e* 104 (M^+ − HCl). A picrate was prepared in the same manner as for the nondeuterated compound **4** and showed the same melting point at 195–196 °C.

Hydrogenation of Pyrrolidinone (20). Pyrrolidinone (**20**, 213 mg, 2.5 mmol) and PtO_2 (342 mg, 1.25 mmol) were hydrogenated as before in 1 N HCl (50 mL). No reaction was apparent by ^1H NMR after 47 h at room temperature. The reaction was then heated at 60°C as described above for 88 h, after which time ^1H NMR and ^{13}C NMR (see below) showed the starting pyrrolidinone to be gone, and in its place a new product which, after filtration and evaporation, appeared as a crystalline solid: mp 133–135 °C; ^1H NMR pyrrolidinone δ 3.5 (5, t H), 2.2 (m, 4 H); hydrogenation product δ 3.0 (t, 2 H), 2.5 (t, 2 H), 2.0 (q, 2 H); ^{13}C NMR hydrogenation product δ 177.6 (s), 38.8 (t), 31.2 (t), 22.2 (t).

By comparison of melting points and NMR with that of an authentic sample, the product recovered from the hydrogenation reaction was established as γ-aminobutyric acid hydrochloride (**21**).

Registry No.—**3**, 19230-81-0; **4**, 67316-70-5; DL-**5a**, 302-72-7; L-**5a**, 56-41-7; **5b**, 63-91-2; DL-**6a**, 67337-40-0; L-**6a**, 1758-74-3; **6b**, 13551-04-7; **7a**, 67316-71-6; **7b**, 67316-72-7; **8a**, 67316-73-8; **9**, 15231-28-4; **10**, 26893-39-0; **18**, 5699-40-1; **18** HCl, 39270-72-9; **20**, 616-45-5; **23** HCl, 67316-74-9; **23** picrate, 67316-76-1; *S*-methylisothiourea sulfate, 867-44-7; β-alanine, 107-95-9.

References and Notes

(1) R. Greenhalgh and R. A. B. Bannard, *Can. J. Chem.*, **39**, 1017 (1961).
(2) K. Matsumoto and H. Rapoport, *J. Org. Chem.*, **33**, 552 (1968).
(3) J. F. Stearns and H. Rapoport, *J. Org. Chem.*, **42**, 3608 (1977).
(4) For example, B. Wojcik and H. Adkins, *J. Am. Chem. Soc.*, **56**, 2419 (1934).
(5) M. M. Wegner and H. Rapoport, *J. Org. Chem.*, **42**, 3065 (1977).
(6) F. H. Holm, *Arch. Pharmacol.*, **242**, 612 (1904).
(7) Described as "Alkaline ferricyamide–nitroprusside" in Block, Durrum, and Zweig, "Paper Chromatography and Paper Electrophoresis", Academic Press, New York, N.Y., 1958, p 348.
(8) A. J. McAlees and R. McCrindel, *J. Chem. Soc.*, 2425 (1969).
(9) R. McCrindle, K. H. Overton and R. A. Raphael, *J. Chem. Soc.*, 4798 (1962).
(10) J. V. Rodricks and H. Rapoport, *J. Org. Chem.*, **36**, 46 (1971).
(11) (a) H. King, *J. Chem. Soc.*, 2374 (1930); (b) I. S. Bengelsdorf, *J. Am. Chem. Soc.*, **75**, 3138 (1953).
(12) Melting points were measured in an open capillary and are corrected. ^1H NMR spectra were taken at 60 MHz in D_2O using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard (δ 0) or Me_4Si in a concentric insert as an external standard (δ 0). ^{13}C NMR spectra were taken at 25.14 MHz in D_2O using dioxane as an internal standard (δ 66.5). Off resonance decoupling was used to determine the ^{13}C NMR multiplicities. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley, Calif. All hydrogenations were carried out at room temperature unless otherwise noted and all evaporations were done in vacuo using a Berkeley Rotary Evaporator.
(13) R. Pant, *Z. Physiol. Chem.*, **335**, 272 (1964).
(14) A. F. McKay and M. E. Kreling, *J. Org. Chem.*, **22**, 1581 (1957).
(15) L. S. Hafner and R. Evans, *J. Org. Chem.*, **24**, 1157 (1959).

Synthesis of 1-Substituted Tricyclo[3.3.1.0^{2,7}]nonanes

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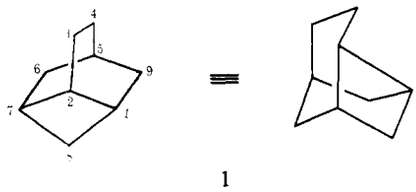
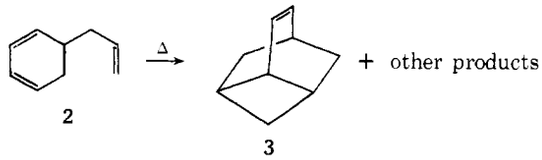
1-Acetyltricyclo[3.3.1.0^{2,7}]non-3-ene (**15**) has been prepared by a five-step reaction sequence from 3-*endo*-carboxybicyclo[3.3.1]non-6-ene. The skeletal framework of **15** follows from its conversion to the parent hydrocarbon, tricyclo[3.3.1.0^{2,7}]nonane. Alternative conditions for the epimerization of 3-*endo*-acetylbicyclo[3.3.1]non-6-ene have been determined.

Although the synthesis of tricyclo[3.3.1.0^{2,7}]nonane (**1**) has not been reported previously, two independent routes leading to compounds which contain this carbon skeleton are

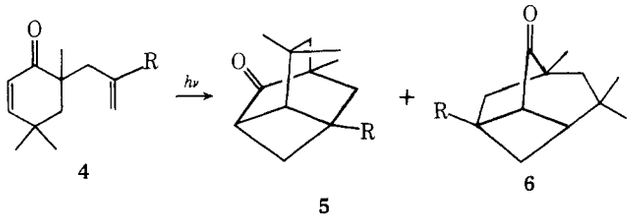


1

known. In 1967 Krantz noted that pyrolysis of 5-allylcyclohexa-1,3-diene (**2**) at 225 °C gives tricyclo[3.3.1.0^{2,7}]non-3-ene (**3**) as well as 1-allylcyclohexa-1,3-diene, 2-allylcyclohexa-1,3-diene, benzene, and recovered starting material.[2] Through labeling studies it was established that **3** is formed from **2** at 184 °C by a [4 + 2] cycloaddition mechanism.[3] At higher temperatures at least one other mechanistic pathway becomes competitive.[3] More recently, Fröstl and Margaretha have found that irradiation of various 6-allyl-4,4,6-trimethyl-2-cyclohexenones (**4**) gives mixtures of the isomeric tricyclononanones **5** and **6**.[4] The product ratio depends on the substituent R of the allylic side chain and is somewhat influenced by the solvent.[4] We now wish to report an alternative synthesis of the tricyclo[3.3.1.0^{2,7}]nonane skeleton which permits the



2 **3**



4 **5** **6**

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