Dicyclohexano[b,e]pyrazine[36] (**15**).—Using the procedure outlined above for the preparation of **14**, 2.02 g (13.5 mmol) of **3c** was converted to 0.443 g (35%) of crude **15**. Sublimation of the crude product at 55° (0.005 mm) gave 0.375 g (30%) of **15** as white, irregular, crystalline clusters: mp 107–108° (lit. mp 109.6–110.6[9] and 108–109°);[37] ir (KBr) 1390 and 1435 cm^{-1}; nmr (CCl_4) δ 1.85 (bs, 1, C-2, C-3, C-7, and C-8 H) and 2.78 ppm (bs, 1, C-1, C-4, C-6, and C-9 H).

As above, there was also isolated 0.748 g (38%) of crude acipic acid, mp 138–146°. Recrystallization from benzene gave 0.354 g (18%) of adipic acid: mp 149–153°; ir (KBr) identical with that of an authentic sample, mp 150–154°; mmp 149–156°.

Androstan-17β-ol-2,3-dione Monohydrate (**17**).—Using a procedure described earlier,[25] 0.285 g (0.892 mmol) of **6b** was treated with 3.5 g (0.028 mmol) of sodium sulfite in 15 ml of glacial acetic acid. Isolation of the product in the usual way[25] gave 0.076 g (26%) of crude **17**. Recrystallization from ethanol–water gave 0.027 g (9%) of **17** monohydrate: mp 161–164° dec (lit.[24] mp 232–234°, not hydrated, recrystallized from chloroform); uv max (absolute C_2H_5OH) 270 nm (ϵ 6400); nmr ($CDCl_3$) δ 0.77 (s, 3, C-18 or C-19 H), 1.05 (s, 3, C-18 or C-19 H), 5.71 (d, 0.2, J = 3.0 Hz, C-4 H of **17b**), and 6.39 ppm (s, 0.8, C-1 H of **17a**).

Anal. Calcd for $C_{19}H_{28}O_3 \cdot H_2O$: C, 70.77; H, 9.38; mol wt, 322.43. Found: C, 71.02; H, 9.33; mol wt (mass spectrum), 305 ($M^+ - H_2O + 1$ = 305.42), 304 ($M^+ - H_2O$).

(1*R*,3*S*)-3-Salicylidenimino-2-bornanone (**20**).—To a mixture of 25 ml of water, 25 ml of ether, and 0.498 g (2.44 mmol) of **4c** was added 8 ml of 10% aqueous sodium hydroxide. The layers were separated, and the aqueous layer was extracted with four 25-ml portions of ether. The combined ethereal solutions were washed with water, dried (K_2CO_3), and filtered. To this solution was added 3.5 ml of absolute ethanol containing 2.9 mmol of salicylaldehyde. The solvent was evaporated. The crystalline residue was recrystallized from methanol, and there was obtained 0.313 g (47%) of **20**, mp 103–105°. After sublimation at 90° (0.005 mm), there was obtained 0.285 g (43%) of **20** as yellow platelets: mp 107–108°; $[\alpha]^{25}D$ −170° (*c* 0.828, CH_3OH); ir (KBr) 1630 (C=N) and 1750 cm^{-1} (C=O); nmr (CCl_4) δ 0.91 and 1.01 (two s, 6 and 3, respectively, C-8, C-9, and C-10 H), 3.85 (d, 1, J = 4.5 Hz, C-3 H), 7.01 (m, 4, aromatic H), 8.50 (s, 1, CH=N), and 12.06 ppm (s, 1, OH).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.58; H, 7.82; N, 5.19.

Methyl 16,17-*seco*-5α-Androstan-3β-ol-16-oate-17-oic Acid (**21**).—A 10% excess of 10% aqueous sodium hydroxide was added to a solution of 0.303 g (0.886 mmol) of **7c** in 50 ml of methanol. The mixture was stirred overnight, diluted with water, and then thoroughly extracted with ether. Evaporation of the ether gave only a trace of residue. The aqueous solution was acidified with 2 *N* hydrochloric acid and again thoroughly extracted with ether. This ethereal solution was dried (Na_2SO_4), and evaporation of the ether gave 0.271 g of residue, mp 95–145°. Two recrystallizations of this solid from ethanol–water gave 0.082 g (26%) of **21** as very fine, white needles, mp 189–190°. Sublimation at 150° (0.005 mm) gave **21**: mp 183–184°; $[\alpha]^{22}D$ −90° (*c* 0.36, absolute C_2H_5OH); ir (KBr) 1715 (C=O), 2600 (CO_2H), and 3410 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.78 (s, 3, C-18 or C-19 H), 1.10 (s, 3, C-18 or C-19 H), 1.98 (s, 3, OCH_3), and 4.64 ppm (bs, 2, OH, disappeared on shaking with D_2O); mass spectrum *m/e* (% of base peak, assignment) 352 [11, **22** (M^+)], 278 (23, **24**), 74 (34, **23**).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15; mol wt, 352.46. Found: C, 68.38; H, 9.30; mol wt (mass spectrum), 352.

Registry No.—**1b**, 31571-12-7; **1c**, 5440-22-2; **2b**, 31579-37-0; **2c**, 5464-16-4; **3c**, 6946-05-0; **4a**, 464-49-3; **4b**, 31571-14-9; **4c**, 31638-54-7; **5b**, 31571-15-0; **6a**, 521-18-6; **6b**, 31571-17-2; **6c**, 20985-72-2; **7a**, 481-29-8; **7b**, 31615-29-9; **7c**, 31571-20-7; **8a**, 53-41-8; **8b**, 31571-22-9; **8c**, 31571-23-0; **8d**, 31571-24-1; **9**, 7768-89-0; **10**, 31571-26-3; **11**, 30590-92-2; **12**, 20985-93-7; **13**, 31571-28-5; **14**, 31579-41-6; **15**, 4006-50-2; **17a**, 31571-29-6; **17b**, 31571-30-9; **20**, 31571-31-0; **21**, 31615-30-2; 16β-salicylidenimino-5α-androstan-3α-ol-17-one, 31571-32-1.

Reactions of Amines. XVII. The Oxidation of α-Substituted α-Amino Ketones with Lead Tetraacetate[1,2]

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The oxidation of several α-substituted α-amino ketones with lead tetraacetate (or iodosobenzene diacetate) resulted in cleavage of the molecule between the carbonyl and carbinamine functions, yielding acid derivatives derived from the acyl moiety of the molecule and nitriles derived from the carbinamine moiety. In the presence of an alcohol moderate yields of ester and nitrile were obtained. In the absence of alcohol the yield of cleavage products was lower and acetylation of the amino ketone became a more competitive reaction. The oxidation of 2-amino-3,3-dimethyl-1-indanone (**11**) gave a moderate yield of 1,1-dimethylhomophthalic anhydride presumably derived from an intramolecular of an intermediate such as **12**.

This communication is the fifth[3] in a series directed toward the study of the oxidation of organic nitrogen compounds. Several of the next papers in this series will be concerned with the oxidation of nitrogen analogs of the 1,2-glycols[4] and α-hydroxy ketones[4] in which one or more carbon or oxygen atoms have been replaced by nitrogen. For purposes of later comparisons it is necessary to know first how simple analogs, such as the α-amino ketones, behave toward selected oxidants. In this paper the oxidation of *α-substituted* α-amino ketones with lead tetraacetate and iodosobenzene diacetate is discussed.

On the basis of the known, but imperfectly studied, cleavage of 1,2-amino alcohols to carbonyl compounds and imines (or nitriles) on oxidation with lead tetraacetate (eq 1)[4-6] and the known cleavage of α-hydroxy ketones to carbonyl compounds and acid derivatives with the same reagent (eq 2), it might be expected that

(1) Paper XVI: H. E. Baumgarten, R. D. Clark, L. S. Endres, and L. D. Hagemeier, *Tetrahedron Lett.*, 5033 (1967).

(2) This work was supported in part by Public Health Service Research Grant GM-13122 from the National Institute of General Medical Sciences and a National Aeronautics and Space Administration traineeship for H. W. T.

(3) (a) H. E. Baumgarten, P. L. Creger, and R. L. Zey, *J. Amer. Chem. Soc.*, **82**, 3977 (1960); (b) H. E. Baumgarten, A. Staklis, and E. Miller, *J. Org. Chem.*, **30**, 1203 (1965); (c) H. E. Baumgarten and A. Staklis, *J. Amer. Chem. Soc.*, **87**, 1141 (1965); (d) H. E. Baumgarten, W. F. Wittman, and G. J. Lehmann, *J. Heterocycl. Chem.*, **6**, 333 (1969).

(4) R. Criegee and C. A. Bunton in "Oxidations in Organic Chemistry," K. B. Wiberg, Ed., Part A, Academic Press, New York, N. Y., 1965, pp 277–366.

(5) J. Bollinger, Thesis, University of Marburg, Germany, 1937; cited in ref 4.

(6) H. J. Roth and A. Brandau, *Arch. Pharm. (Weinheim)*, **293**, 27 (1960).

$$RCHOHCHNH_2R' \xrightarrow{LTA} [RCHO + R'CH{=}NH] \xrightarrow{LTA} RCHO + R'CN \quad (1)$$

$$RCOCHOHR' \xrightarrow[R''OH]{LTA} RCO_2R'' + R'CHO \quad (2)$$

an α-substituted α-amino ketone would undergo a similar reaction to yield a nitrile (or imine) and an acid derivative (eq 3).

$$RCOCHNH_2R'' \xrightarrow[R''OH]{LTA} [RCO_2R'' + R'CH{=}NH] \xrightarrow{LTA} RCO_2R'' + R'CH \quad (3)$$

Furthermore, since Baer[7] has shown that oxidations of α-hydroxy ketones (eq 2) with lead tetraacetate are markedly accelerated by the addition of alcohols, it might be expected that oxidation of α-amino ketones would be similarly affected by added alcohol.

Although in some oxidations the principal difference between lead tetraacetate (LTA) and iodosobenzene diacetate (IBDA) as oxidants appears to be the greater oxidizing power of the former,[4] it will be shown later in this series that the two reagents can and frequently do lead to a substantially different array of products. For this reason, iodosobenzene diacetate has been included in the present study. Also, in some oxidations to be described in this series, particularly where more than 1 mol of lead tetraacetate appears to be required as oxidant, the optimum yield of a specific product may be obtained with substantially less than the theoretical amount of oxidant or may depend strongly on the order and rate of addition of reactants or on the temperature. Probably this is because of the greater or lesser effects of the competing side reactions (acetylation, acetoxylation, further oxidation, etc.) so common with lead tetraacetate. Examples of these effects will be further documented in various papers in this series. In the present study our interest has been in the course of the reactions and the nature of the products, and we have not tried to optimize either the ratios of reactants or the conditions. Instead, we have used either the theoretical or half the theoretical amount of oxidant and the mildest set of conditions leading to complete reaction of the *oxidant* in a reasonable length of time.

It has been observed also that the rate and course of lead tetraacetate oxidations in nonprotic solvents are affected by the presence of certain added acids and bases. For example, the initial rates of oxidation of amines[8] and of *N*-arylbenzohydroxamic acids[9] are depressed by addition of acetic acid. We have not studied the possible effects of added acids or bases, but it should be noted that our experiments were conducted with the hydrochloride of the amino ketone (because of the instability of the free amino ketone) and that varying amounts of acetic acid were formed during the course of these oxidations.

In substantial accord with the above expectations oxidation of α-aminovalerophenone (**1a**) hydrochloride with 1 or 2 mol of lead tetraacetate in methylene chloride containing some alcohol (methanol or ethanol) gave a mixture which contained 3–5% of benzoic acid (**8a**), 46–58% of alkyl benzoate (**3a**), 0–5% of acetic benzoic anyydride (**5a**), 40–54% of *n*-butyronitrile (**6a**), and 0–21% of *N*-acetyl-α-aminovalerophenone (**7a**) (Table I). Products **3a**, **5a**, **6a**, and **7a** may be rationalized by the mechanism shown in Scheme I, which may be regarded as derived from a contemporary version of the Baer mechanism for the oxidation of α-hydroxy ketones under similar conditions.[4,7] The principal difference between the mechanism shown here and that of Baer is that in the Baer mechanism the alcohol adds to the carbonyl group *before* attack by the oxidant. In some alcohol-assisted oxidations[10,11] the prior addition of alcohol appears unlikely. Furthermore, in contrast to the results of Baer, oxidation does take place in the absence of alcohol, although with lower yields of acid derivatives. These results suggest that prior addition of alcohol is not a requirement although such addition may provide an alternative path for oxidation.

It is also possible that the ester **3** could have formed in whole or in part by reaction of **5a** with methanol. The small amount of benzoic acid may have resulted from traces of water in the solvents reacting with **2a** prior to cleavage or with **5a** after cleavage. The amide **7a** could have resulted from the reaction of **1a** and **5a** although direct acetylation with lead tetraacetate, or some species derived therefrom, is a likely alternative because significant amounts of **7a** were obtained in only those oxidations in which a solution of **1a** in methylene chloride–methanol was added to solid lead tetraacetate (rather than to a solution of lead tetraacetate in methylene chloride).

To resolve some of these ambiguities, several oxidations of *p*-chloro- and *p*-methyl-α-aminopropiophenone hydrochlorides with lead tetraacetate were carried out in the presence and absence of added alcohol and the reaction mixtures were worked up in such a way as to convert any anhydride formed to acid. The results of these experiments are also given in Table I. In these experiments the yields of acid derivatives (**3** plus **8**) are much greater in the presence than in the absence of added alcohol. Furthermore, the yields of acetylated amino ketone **7** in the experiments without added alcohol are greater than the yields of acid **8**. These results suggest (1) that, in partial accord with the conclusions of Baer,[7] the ester formed on oxidation is derived largely from an intermediate such as **2** rather than entirely from the reaction of an anhydride (such as **5**) with the alcohol present and (2) that acetylation of the unreacted amino ketone must involve in part some species other than the mixed anhydride (such as **5**), probably some species derived from lead tetraacetate.

Oxidation of the hydrochloride of the cyclic α-amino ketone, α-aminocyclohexanone (**9**), with lead tetraacetate in methylene chloride containing ethanol gave a 50% yield of ethyl δ-cyanovalerate (**10**), but oxidation of the hydrochloride of 2-amino-3,3-dimethyl-1-indanone (**11**) under similar conditions gave a mixture of α-(*o*-carboethoxyphenyl)isobutyronitrile (**15**), 1,1-dimethylhomophthalic anhydride (**13**), and N-acetylated amino ketone **14** in the ratio (by nmr analysis)

(7) E. Baer, *J. Amer. Chem. Soc.*, **62**, 1597 (1940); **64**, 1416 (1942).
(8) A. Stojiljhovic, V. Andrejevic, and M. L. Mihailovic, *Tetrahedron*, **23**, 721 (1967).
(9) L. K. Dyall, J. O. M. Evans, and J. E. Kemp, *Aust. J. Chem.*, **21**, 409 (1968).
(10) J. B. Aylward and R. O. C. Norman, *J. Chem. Soc. C*, 2399 (1969).
(11) H. E. Baumgarten, H. W. Taylor, C. D. Campbell, C. T. Watts, and D. J. Maitland, unpublished results.

TABLE I

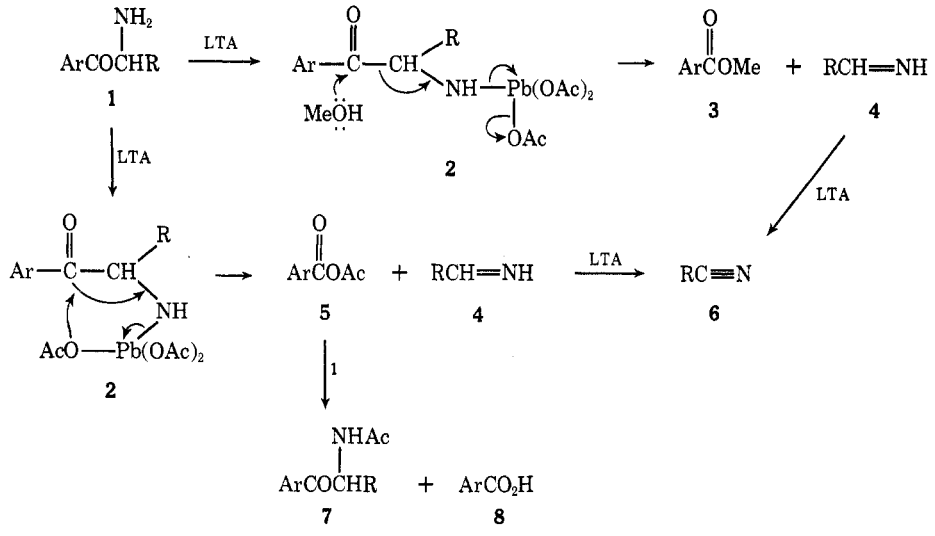
OXIDATIVE CLEAVAGE OF α-AMINO KETONES

$$ArCOCH(NH_2)R \xrightarrow[R'OH]{[O]} ArCO_2H + ArCO_2R' + RCN + ArCOCHR$$
$$\quad 1 \qquad\qquad\qquad 8 \qquad\quad 3 \qquad\quad 6 \qquad\quad 7 \qquad\quad NHAc$$

Ar	R	Oxidant[a]	Solvent	% yield 8	3	6	7
C_6H_5	n-C_3H_7	1 LTA	CH_2Cl_2–EtOH	3.1	58	49	0
		1 LTA	CH_2Cl_2–MeOH		59	49	0
		2 LTA	CH_2Cl_2–EtOH	5.5	48	54	0
		2 LTA	CH_2Cl_2–MeOH	5	46	40	22
		2 IBDA	CH_2Cl_2–MeOH		17	19	40
		2 $NaIO_4$	MeOH	50	11	(62)[b]	
p-$CH_3C_6H_4$	CH_3	1 LTA	CH_2Cl_2	46	0		35
		1 LTA	$CHCl_3$–EtOH	19	43		10
		2 LTA	$CHCl_3$–EtOH	40	24	64	
		2 IBDA	$CHCl_3$–EtOH	29	15	94	0
p-ClC_6H_4	CH_3	1 LTA	CH_2Cl_2	28	0		41
		1 LTA	$CHCl_3$–EtOH	28	54		30

[a] LTA = lead tetraacetate; IBDA = iodosobenzene diacetate. Number indicates number of molar equivalents of oxidant per mole of α-amino ketone. [b] n-Butyric acid.

SCHEME I

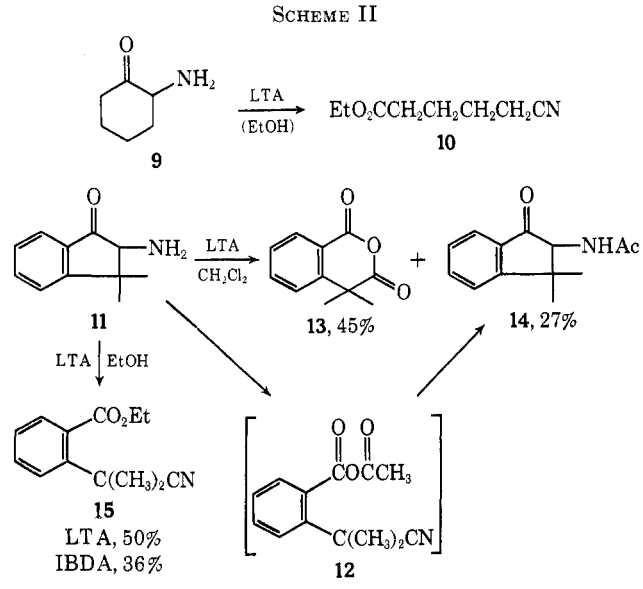


a, Ar = C_6H_5; R = n-C_3H_7
b, Ar = p-$CH_3C_6H_4$; R = CH_3
c, Ar = p-ClC_6H_4; R = CH_3

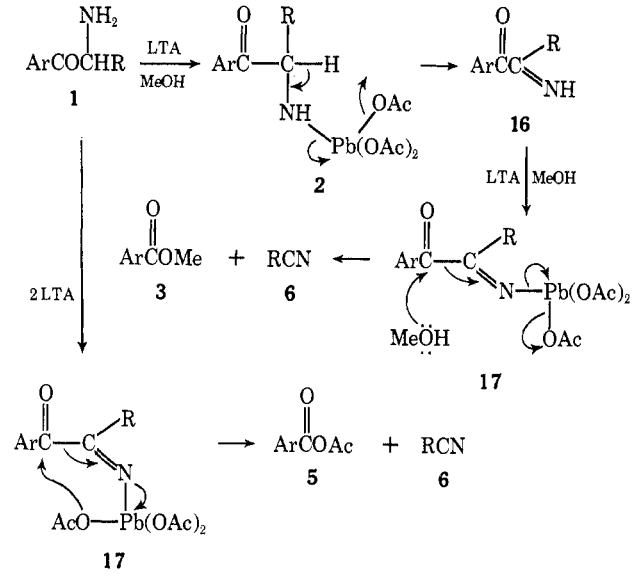
of 3:2:3. Oxidation of **11** in the absence of alcohol gave a 45% yield of **13** and 27% of **14**. These results are consistent with those from the acyclic ketones provided that it is assumed that the anhydride **13** arose from the intramolecular cyclization of an intermediate cyano ester **15** or, more probably, because of the high yield of **13** in alcohol-free methylene chloride, a cyano anhydride **12** (Scheme II).

All of the foregoing oxidation results are consistent with the simple overall picture of the reaction shown in Scheme I. However, these experiments do not distinguish between reasonable alternative mechanisms, those based solely on the analogy with α-hydroxy ketones (Scheme I) and those taking cognizance of the special properties of amines and imines (Scheme III). Although on the basis of the principle of conservation of mechanism the invocation of alternative mechanisms like that in Scheme III may appear unnecessary and perhaps undesirable, it will be shown in later papers in this series that oxidations proceeding by se-

SCHEME II

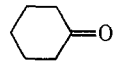
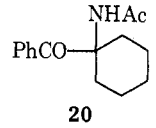


SCHEME III



quences related to that shown in Scheme III may be realized in the laboratory.

Oxidation of α-aminocyclohexyl phenyl ketone (**18**) hydrochloride, which cannot react by the route shown in Scheme III, with lead tetraacetate in chloroform solution containing some ethanol gave a 62% yield

	PhCO₂Et **6a**	+ PhCO₂H **8a**	+  **19**	+  **20**
LTA	44%	22%	62%	20%
IBDA	17%		30%	40%

of cyclohexanone (**19**), 44% of ethyl benzoate (**6a**), and 22% of benzoic acid (**8a**).[12] Thus, it appears that *α-substituted* α-amino ketones react with lead tetraacetate in a manner very much like that of α-hydroxy ketones.[7] In a later paper in this series this conclusion will be contrasted with quite different observations for other N analogs of the α-hydroxy ketones.

As noted above, most of the oxidations described here were carried out with both lead tetraacetate and iodosobenzene diacetate. In these experiments (but not necessarily those to be described in later papers) the principal observed differences between the two oxidants were lower yields of acid derivatives (and higher yields of N-acetylated amino ketone) and slower reactions with iodosobenzene diacetate. The yield differences are shown in the tables and equations. α-Aminovalerophenone hydrochloride was also oxidized with sodium periodate in methanol to yield 50% of benzoic acid, 11% of methyl benzoate, and 62% of *n*-butyric acid.

(12) Some N-acetylated α-amino ketone (**20**) was also present but the procedure used was not suitable for accurate determination of the yield of this product.

Experimental Section[13]

Oxidation of α-Aminovalerophenone.—The following procedure is typical of that employed in this study.

A solution of 0.500 g (0.00235 mol) of α-aminovalerophenone hydrochloride[10] in 10 ml of methylene chloride and 3 ml of dry ethanol was added dropwise over a period of 3 min to a solution of 2.08 g (0.00470 mol) of lead tetraacetate in 7 ml of dry methylene chloride at room temperature under nitrogen. The reaction mixture was accompanied with a slight yellow color change and the immediate deposition of lead salts. The solution was allowed to stir for 30 min after which time a negative starch iodide test was obtained. The reaction mixture was filtered through Celite (to remove lead salts) and a small aliquot of the filtrate was analyzed by glc using cyclohexanone as an internal standard and a 2-m column of OV-1 silicone oil at 55° (*n*-butyronitrile) and 90° (ethyl benzoate). The analysis indicated the following yields: *n*-butyronitrile, 0.087 g (54%);[14,15] ethyl benzoate, 0.169 g (48%).[4,15]

The remainder of the filtrate was extracted with saturated aqueous sodium bicarbonate. The aqueous layer was acidified with hydrochloric acid and extracted with three 25-ml portions of ether. Evaporation of the ether gave 0.015 g (5.5%)[14] of benzoic acid.

The Celite–lead salts mixture was extracted with 30% aqueous sodium hydroxide. Neutralization with hydrochloric acid, extraction with ether, and evaporation of the ether yielded a trace of benzoic acid, identified by comparison of its infrared spectrum with that of an authentic sample.

Evaporation of the dried organic layer from the bicarbonate extraction to approximately 1 ml followed by analysis by column chromatography (15 g of fluorosil) yielded no new identifiable products. A yellow residue (0.07–0.08 g) remained.

The above procedure was repeated using half the stated amount of lead tetraacetate (1.04 g, 0.00235 mol) in 7 ml of methylene chloride. The yields of products follow: *n*-butyronitrile, 0.080 g (49%);[15,16] ethyl benzoate, 0.206 g (58%);[15,16] benzoic acid, 0.009 g (3.1%);[16] residue 0.05–0.06 g.

No N-acetylated amino ketone could be found in the reaction mixtures from either of the above experiments.

A solution of 1.00 g (0.0047 mol) of α-aminovalerophenone hydrochloride[17] in 5 ml of methylene chloride and 5 ml of methanol was added in one portion with stirring to 4.4 g (0.01 mol) of dry lead tetraacetate. The solution, which became bright yellow for about 30 sec and then colorless, was stirred for 20 min and filtered. The filtrate was extracted with 25 ml of 10% aqueous sodium carbonate and then with 25 ml of 2 *N* hydrochloric acid. The solution was dried ($MgSO_4$) and evaporated. An aliquot of the pale yellow residual liquid was analyzed by glc using cyclohexanone as a standard and a column of 25% silicone oil on Chromosorb at 100°. The analysis indicated the following yields:[14,15] *n*-butyronitrile, 40%; methyl benzoate, 46%; and acetic benzoic anhydride, 5%. Dilution of the liquid residue with 100 ml of petroleum ether yielded 0.23 g (22%) of α-acetaminovalerophenone (**7a**), mp 59–59.5°.

Acidification of the basic extract yielded a trace of benzoic acid, mp 122°, the infrared spectrum identical with that of an authentic sample.

An authentic sample of **7a** was prepared by adding 0.36 ml (0.005 mol) of acetyl chloride dropwise with stirring to a solution of 1.00 g (0.005 mol) of α-aminovalerophenone hydrochloride in 20 ml of pyridine. The mixture was stirred for 5 min, diluted with 30 ml of chloroform, extracted with two 50-ml portions of 2 *N* hydrochloric acid, dried ($MgSO_4$), and evaporated. The resulting oil was chromatographed on Florisil, the chloroform eluate yielding 0.80 g (83%) of α-acetaminovalerophenone: mp 59–59.5°; ir (CH_2Cl_2) 3450 (NH), 1704 (ketone C=O), and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.15–8.00 (m, 6, aromatic and NH protons), 5.55 (5, 1, J = 6 Hz, COCHN), 2.05 (s, 3, CH_3CO), and 0.70–1.70 (m, 7, aliphatic protons).

(13) Analyses by Micro-Tech Laboratories, Skokie, Ill.

(14) Based on amino ketone; expected maximum yield is 100%.

(15) Data from the calibration runs indicated that the glc analyses could be expected to have precision of ±1% for esters and ±3% for nitriles and accuracy of ±3% for esters and ±5% for nitriles.

(16) Based on amino ketone. Since only 1 equiv of oxidant was used, the expected maximum yield would be 50% *if both oxidative steps proceeded to completion.*

(17) H. E. Baumgarten, J. E. Petersen, and D. C. Wolf, *J. Org. Chem.*, **28**, 2369 (1963).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.19; H, 7.76; N, 6.15.

α-Aminovalerophenone hydrochloride (1.00 g, 0.0047 mol) was oxidized as described above using 2.22 g (0.005 mol) of lead tetraacetate. Work-up of the reaction and analysis by glc as described above gave the following yields:[15,16] *n*-butyronitrile, 49%; methyl benzoate, 59%.

To a solution of 3.32 g (0.01 mol) of iodosobenzene diacetate in 10 ml of dry methylene chloride was added a slurry of 1.00 g (0.0047 mol) of α-aminovalerophenone hydrochloride in 10 ml of dry methylene chloride and 5 ml of methanol. The solution was heated under reflux for 4 hr, cooled, extracted with 25 ml of 10% sodium carbonate solution and 25 ml of 2 *N* hydrochloric acid solution, dried ($MgSO_4$), and analyzed by glc as described above. The analysis indicated the following yields:[14,15] *n*-butyronitrile, 19%; methyl benzoate, 17%.

The solution was then evaporated yielding a brown oil. Petroleum ether (bp 30–60°) was added and the solution was evaporated again in order to remove most of the iodobenzene. This procedure was repeated twice and then petroleum ether was again added to the oil and the mixture was shaken for a few minutes. The petroleum ether solution was decanted and the resulting oil warmed (100°) in the rotary evaporator for 2 hr. The brown oil solid which crystallized on cooling was recrystallized from ether–petroleum ether, yielding 0.41 g (40%)[14] of *N*-acetyl-α-aminovalerophenone.

To a solution of 1.00 g (0.004 mol) of α-aminovalerophenone hydrochloride in 20 ml of methanol was added 1.72 g (0.008 mol) of sodium metaperiodate, and the solution was stirred overnight. The solution was filtered, diluted with water, and extracted with ether. The ether solution was extracted with 50 ml of 2 *N* hydrochloric acid and then with 50 ml of 10% sodium carbonate solution and dried ($MgSO_4$). Analysis by glc (60°) showed a trace of butyraldehyde to be present and 0.06 g (11%)[14,15] of methyl benzoate (methyl phenylacetate was added as a standard).

The basic extract was acidified and extracted with ether. The ether was evaporated and the resulting oily product was esterified[18] and analyzed by glc using cyclohexanone as a standard, indicating (at 100°) a 50% yield[14,15] of benzoic acid and (at 60°) a 62% yield[14,15] of butyric acid.

Oxidation of α-Amino-*p*-methylpropiophenone. A. Ethanol Present.—To a stirred solution of 2.25 g (0.005 mol) of lead tetraacetate in 20 ml of ethanol-stabilized chloroform was added a slurry of 1.00 g (0.005 mol) of α-amino-*p*-methylpropiophenone hydrochloride[19] in 20 ml of chloroform, and the solution was stirred for 5 min. The solution was diluted with 50 ml of ether, the lead salts were filtered off, and the filtrate was extracted with 50 ml of 10% aqueous sodium carbonate solution. The organic layer was dried ($MgSO_4$) and the solvent was evaporated leaving a brown oil. Chromatography of the oil on Florisil yielded, with ether, 0.35 g (43%)[16] of ethyl *p*-toluate (identified by glc, ir, and nmr), and with chloroform, 0.10 g (10%)[14] of α-acetamino-*p*-methylpropiophenone (**7b**), mp 65–66°.

The alkaline extract was acidified and filtered, yielding 0.13 g (19%)[16] of *p*-toluic acid, mp 179°, which was identified by comparison of its infrared spectrum with that of an authentic sample.

An authentic sample of **7b** was prepared as described above for α-acetaminovalerophenone: yield 77%; mp 66–66.5°; ir (CH_2Cl_2) 3450 (NH) and 1675 cm^{-1} (broad, amide + ketone C=O); ir (KBr) 1690 (ketone C=O) and 1670 cm^{-1} (amide C=O); nmr (CCl_4) δ 7.90 and 7.27 (d, 4, J = 8 Hz, aromatic protons), 5.45 (quartet, 1, J = 7 Hz, CH_2), 2.40 (s, 3, *p*-CH_3), 1.98 (s, 3, CH_3CO), and 1.23 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.24; H, 7.32; N, 6.54.

In another experiment a solution of 1.00 g (0.005 mol) of α-amino-*p*-methylpropiophenone hydrochloride in 20 ml of chloroform and 5 ml of absolute ethanol was added to 4.50 g (0.01 mol) of lead tetraacetate, and the resulting solution was stirred for 10 min, filtered, and extracted successively with 20 ml of 10% aqueous sodium carbonate, 20% sulfuric acid, and water. Analysis of the dried ($MgSO_4$) organic layer by glc at 75° (acetonitrile) and 125° (ethyl *p*-toluate) using cyclohexanone as an internal standard and a column of 20% silicone oil on Chromosorb R indicated that the mixture contained 0.13 g (64%)[14,15] of acetonitrile and 0.17 g (24%)[14,15] of ethyl *p*-toluate. Acidification of basic extract gave 0.27 g (40%)[14] of *p*-toluic acid. The infrared spectrum of the organic layer showed that a small amount of an anhydride was probably present.

B. Ethanol Absent.—To 2.25 g (0.005 mol) of lead tetraacetate was added a solution of 1.00 g (0.005 mol) of α-amino-*p*-methylpropiophenone hydrochloride in 30 ml of dry methylene chloride. The mixture was stirred for 1 hr and filtered. The filtrate was extracted with 50 ml of 10% aqueous sodium carbonate, dried ($MgSO_4$), and evaporated, yielding 0.36 g (35%)[14] of α-acetamino-*p*-methylpropiophenone, mp 66–66.5°. The aqueous layer was acidified and filtered, yielding 0.31 g (46%)[16] of *p*-toluic acid, mp 179°.

To 2.90 g (0.009 mol) of iodosobenzene diacetate was added a solution of α-amino-*p*-methylpropiophenone hydrochloride (1.00 g, 0.005 mol) in 20 ml of chloroform and 5 ml of absolute ethanol. The solution was stirred under reflux for 30 min, cooled, extracted successively with 50 ml of 10% sodium carbonate solution and 50 ml of 20% sulfuric acid solution, and dried ($MgSO_4$). To the solution was added cyclohexanone as an internal standard for glc analysis. The analysis for acetonitrile (75°) showed 0.17 g (92%)[14,15] to be present in the oxidation mixture. Analysis for ethyl *p*-toluate (125°) showed 0.10 g (15%)[14,15] to be present in the oxidation mixture. Acidification of the basic extracts yielded 0.21 g (29%))[14] of *p*-toluic acid.

Oxidation of α-Amino-*p*-chloropropiophenone. A. Ethanol Present.—To 2.22 g (0.005 mol) of lead tetraacetate was added a solution of 1.00 g (0.0045 mol) of α-amino-*p*-chloropropiophenone[20] hydrochloride in 35 ml of chloroform (ethanol stabilized). The solution was stirred for 10 min and filtered. The filtrate was extracted with 30 ml of 10% sodium carbonate solution, dried ($MgSO_4$), and evaporated, yielding 0.78 g of brown oil. The oil was taken up in carbon tetrachloride and analyzed by nmr. All of the observed peaks could be attributed to two compounds, ethyl *p*-chlorobenzoate [yield, 0.45 g (48%)][16] and α-acetamino-*p*-chloropropiophenone [yield, 0.30 g (25%)].[16]

A small portion of the mixture was chromatographed on Florisil, the ether eluate yielding pure ethyl *p*-chlorobenzoate (identified by its infrared spectrum) and the chloroform eluent yielding α-acetamino-*p*-chloropropiophenone: mp 106° (lit.[21] mp 106–107°); ir (neat) 3395 (NH), 1695 (ketone C=O), 1660 cm^{-1} (amide C=O); nmr (CCl_4) δ 7.96 and 7.40 (d, 4, J = 8 Hz, aromatic protons), 5.47 (q, 1, J = 7 Hz, CH_2), 1.96 (s, 3, CH_3CO), and 1.30 (t, 3, J = 7 Hz, *p*-CH_3).

Acidification of the basic extract yielded 0.20 g (28%) of *p*-chlorobenzoic acid, mp 241°, the ir spectrum identical with that of an authentic sample.

B. Alcohol Absent.—Oxidation of 1.00 g (0.0045 mol) of α-amino-*p*-chloropropiophenone hydrochloride with 2.22 g (0.005 mol) of lead tetraacetate using the procedure described for α-amino-*p*-methylpropiophenone hydrochloride yielded 0.20 g (28%)[16] of *p*-chlorobenzoic acid and 0.41 g (41%)[14] of α-acetamino-*p*-chloropropiophenone.

Oxidation of 1-Aminocyclohexyl Phenyl Ketone.—A slurry of 1.0 g (0.0042 mol) of 1-aminocyclohexyl phenyl ketone[22] hydrochloride in a solution of 20 ml of chloroform and 5 ml of absolute ethanol was added 2.25 g (0.0050 mol) of lead tetraacetate and the mixture was stirred for 15 min. The mixture was filtered, extracted successively with 25 ml of 10% aqueous sodium carbonate, 35 ml of 20% sulfuric acid, and water, dried ($MgSO_4$), and evaporated. The resulting 0.8 g of yellow liquid was analyzed by glc using iodobenzene as a standard and a column of 20% silicone oil on Chromosorb R at 120° and was found to contain a 59%[14,15] (0.24 g) yield of cyclohexanone and a 44%[14,15] (0.26 g) yield of ethyl benzoate.

Acidification of the alkaline extract yielded 0.10 g (20%)[14] of benzoic acid, mp 122°.

The infrared spectrum (peak at 3400 cm^{-1}, several peaks in C=O region) of the yellow liquid indicated the presence of an *N*-acetyl compound, but this compound could not be isolated in the pure state.

Oxidation of 3,3-Dimethyl-2-amino-1-indanone Hydrochloride. A. In the Absence of Alcohol.—A slurry of 3.0 g (0.014 mol) of

(18) R. O. Clinton and S. O. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).

(19) Prepared in 65% yield by the method of ref 14, mp 223–224° dec. *Anal.* Calcd for $C_{10}H_{14}NOCl$: C, 60.15; H, 7.02; N, 7.02; Cl, 17.79. Found: C, 60.07; H, 7.15; N, 7.07; Cl, 17.93.

(20) Prepared in 33% yield by the method of ref 17, mp 226° dec. *Anal.* Calcd for $C_9H_{11}Cl_2NO$: C, 49.10; H, 5.02, N, 6.36; Cl, 31.96. Found: C, 48.76; H, 5.03; N, 6.59; Cl, 31.84.

(21) H. K. Müller, *Justus Liebigs Ann. Chem.*, **599**, 61 (1956).

(22) Prepared in 27% yield by the method of ref 17, sublimes above 220°. *Anal.* Calcd for $C_{13}H_{18}NOCl$: C, 65.13; H, 7.51; N, 5.84; Cl, 14.82. Found: C, 65.29; H, 7.62; N, 5.73; Cl, 14.85.

3,3-dimethyl-2-amino-1-indanone[23] hydrochloride in 50 ml of dry methylene chloride was added to 6.6 g (0.015 mol) of lead tetraacetate and the mixture was stirred for 30 min, filtered, extracted with 10% aqueous sodium carbonate solution, dried ($MgSO_4$), and evaporated. The resulting brown oil was dissolved in anhydrous ether and cooled overnight, yielding 0.7 g (23%)[14] of *N*-acetyl-3,3-dimethyl-2-amino-1-indanone: mp 116–117°; ir ($CHCl_3$) 3415 (NH), 1730 (ketone C=O), and 1690 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 1.12 (s, 3, CH_3 cis to amide), 1.62 (s, 3, CH_3 trans to amide), 2.13 (s, 3, CH_3CO), 4.75 (d, 1, J = 8 Hz, CH_2), and 7.80 (m, 5, aromatic and amide).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.84; H, 7.00; N, 6.24.

The ether solution was diluted with petroleum ether until the solution became cloudy and cooled overnight, yielding 1.2 g (45%)[16] of 1,1-dimethylhomophthalic anhydride: mp 79° (lit.[24] mp 81–82°); ir ($CHCl_3$) 1800 and 1750 cm^{-1}; nmr ($CDCl_3$) δ 1.76 (s, 6, CH_3) and 7.60 (n, 4, aromatic).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30; O, 25.24. Found: C, 69.77; H, 5.17.

A solution of 1.00 g (0.005 mol) of 2-amino-3,3-dimethyl-1-indanone hydrochloride (0.005 mol) of iodosobenzene diacetate and 30 ml of methylene chloride was heated under reflux for 4 hr. The yellow solution was extracted with 25 ml of 10% sodium carbonate solution, dried, and evaporated, yielding a brown oil. Petroleum ether was added to the oil and the mixture was evaporated to remove iodobenzene. This procedure was repeated several times until the iodobenzene odor no longer was apparent in the sample. The resulting oil (0.7 g) showed infrared absorption (neat) indicating the presence of anhydride (1820 and 1760 cm^{-1}) as well as amide (1690 and 3425 cm^{-1}). The oil was taken up in carbon tetrachloride and analyzed by nmr. The analysis indicated the oil contained 0.3 g (30%)[16] of 1,1-dimethylhomophthalic anhydride and 0.3 g (30%)[16] of 2-acetamino-3,3-dimethyl-1-indanone.

(23) Prepared in 48% yield by the method used by N. Levin, B. Graham, and H. Kolloff, *J. Org. Chem.*, **9**, 380 (1944), for the preparation of 2-aminoindanone, mp 213° dec. *Anal.* Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.62; N, 6.62; Cl, 16.78. Found: C, 62.14; H, 6.73; N, 6.65; Cl, 16.80.

(24) M. Anched and A. Blatt, *J. Amer. Chem. Soc.*, **63**, 1948 (1941).

B. In the Presence of Alcohol.—A slurry of 3,3-dimethyl-2-amino-1-indanone hydrochloride (2.0 g, 0.01 mol) in a solution of 25 ml of methylene chloride and 2.5 ml of ethanol was added to 4.4 g (0.01 mol) of lead tetraacetate. The mixture was stirred for 10 min, filtered, extracted with 10% aqueous sodium carbonate solution, dried ($MgSO_4$), and evaporated. The nmr spectrum of the resulting yellow oil (1.69 g) indicated a 3:3:2 ratio of α-(*o*-carboethoxyphenyl)isobutyronitrile–*N*-acetyl-3,3-dimethyl-2-amino-1-indanone–1,1-dimethylhomophthalic anhydride. The infrared spectrum (film) indicated the presence of nitrile (2240), amide (3425, 1690), ester (1730), and anhydride (1825, 1755 cm^{-1}). Separation of these compounds was not feasible.

Oxidation of α-Aminocyclohexanone Hydrochloride in the Presence of Alcohol.—A slurry of 2.0 g (0.013 mol) of α-aminocyclohexanone hydrochloride in a solution of 25 ml of methylene chloride and 2.5 ml of ethanol was added to 6.2 g (0.014 mol) of lead tetraacetate. The mixture was stirred for 30 min, filtered, extracted with 10% aqueous sodium carbonate solution, dried ($MgSO_4$), and evaporated yielding a brown oil. The oil was taken up in ether and petroleum ether was added until the solution became cloudy. The solution was refrigerated overnight yielding an impure oily solid, which was tentatively identified as α-acetaminocyclohexanone by its infrared and nmr spectra but which could not be completely purified. The remaining solution was evaporated, yielding a pale yellow liquid which was further purified by thin layer chromatography on silica (ether) yielding 0.5 g (25%)[16] of ethyl δ-cyanovalerate,[25] identified by its ir spectrum (neat) 2220 (C≡N) and 1720 cm^{-1} (C=O ester) (lit.[25] 2220, 1720 cm^{-1}), and refractive index $n^{25}D$ 1.436 (lit.[23] 1.44).

Registry No.—**1a**, 31952-46-2; **1b**, 31952-47-3; **1c**, 23933-82-6; **7a**, 31952-49-5; **7b**, 31952-50-8; **7c**, 31952-51-9; **9** HCl, 6946-05-0; **10**, 4450-39-9; **11** HCl, 31952-54-2; **13**, 31952-55-3; **14**, 31999-37-8; **15**, 31952-56-4; **18** HCl, 31952-57-5; lead tetraacetate, 546-67-8.

(25) O. Riobee, M. Lamant, and G. Lancher, *Bull. Soc. Chim. Fr.*, 1535 (1960).

Anodic Oxidations. IV.[1] Electrochemical Oxidation of 2,5-Dimethylthiophene

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Electrochemical oxidations of 2,5-dimethylthiophene in methanol resulted in three types of reactions, depending on the electrolytes used. (1) With ammonium bromide as electrolyte, the product was 3-bromo-2,5-dimethylthiophene exclusively. (2) With nonhalide electrolytes such as ammonium nitrate and sodium acetate, methoxide, and perchlorate, the formation of 2-methoxymethyl-5-methylthiophene was observed. (3) With sodium cyanide, the products were *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrothiophenes (*cis*/*trans* = 2.3), together with comparable amounts of 3-cyano-2,5-dimethylthiophene and 2-methoxymethyl-5-methylthiophene. The bromination involves discharge of the bromide ion at the anode, whereas both the cyanation and methoxylation products are considered to have been derived from initial oxidation of 2,5-dimethylthiophene at the same electrode. Factors controlling the relative prevalence of the two pathways leading to the nuclear cyanation and the side-chain methoxylation are discussed, in reference to the case of 2,5-dimethylfuran studied previously.[1]

The electrochemical behavior of aromatic five-membered heterocycles other than furan still remains to be explored. Previous studies have only enlightened the electrolyses in methanol of thiophene and *N*-methylpyrrole in which methoxylation takes place.[2]

We reported, in a previous paper,[1] that the anodic oxidation of 2,5-dimethylfuran in a methanolic solution of sodium cyanide gave a 2:1 isomeric mixture of *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofurans. The overall reaction involved the initial oxidation of 2,5-dimethylfuran, and proceeded nonstereospecifically. It is known, on the other hand, that, when sodium acetate, sodium methoxide, and ammonium nitrate are used as electrolyte, 2,5-dimethoxy-2,5-dimethyldihydrofuran is produced.[3,4] These contrasting results demonstrate the importance of the electrolyte in electroorganic reactions. There are several other examples in the literature wherein the nature of the electrolytes may be product determining: the anodic methoxylation of furans bearing an electron-withdrawing group must be carried out with sulfuric acid as elec-

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