solution with Amberlite IR-120(H). The equivalent weight was determined by titration of the acidic sirup obtained upon removal of water with standard sodium hydroxide solution. The value obtained was 100 compared to a calculated equivalent weight of 97 for 3-deoxy-2-C-hydroxymethyl-pentaric acid.

Resolution.—An ethanol solution of brucine salts was concentrated to dryness, and the resulting powder was shaken with a little water at 0°. The mixture was then stored for 24 hr. at 0° and centrifuged at 0°. This process was repeated until all the remaining glass was soluble in water at 0°. The crystalline residue which was insoluble in water at 0° had a block m.p. of 163–188° and a X-ray powder diffraction pattern which differed from that of the brucine salt of the acid formed by the action of lime water on a 4-*O*-methyl-D-glucuronate.[11]

3-Deoxy-2-C-hydroxymethyl-L-*erythro*(or L-*threo*)-pentaric Acid.—The above crystalline, but slightly soluble, brucine salt was converted to the free acid with Amberlite IR-120(H), and the sirup obtained by concentration of the solution under reduced pressure at 35–40° was further purified by paper chromatography using the descending method and irrigant B. A component was obtained which appeared as a single component with irrigant B, C and D. This acid had a R_{ga}[16] value of 3.1–3.4 and a R_1[17] value of 1.2–1.3. The purified sirupy, free acid thus obtained (1.46 g.) had 6.4×10^{-3} acid equivalents per gram and $[\alpha]^{25}D$ +5.6° (*c* 1.0, water).

When a portion of this sirup was oxidized with periodate according to the method of Sowden[18] and the formaldehyde was determined by the method of Reeves,[19] 0.5 mole of formaldehyde per equivalent of acid was obtained.

Another portion of the acidic sirup was converted to its brucine salt which was crystallized from ethanol. The crystals had a block m.p. of 192–193°, a capillary m.p. of 177–186° and $[\alpha]^{25}D$ −18.0° (*c* 3.4, water).

Anal. Calcd. for $C_{52}H_{62}O_{15}N_4$: C, 63.6; H, 6.4; N, 5.7. Found: C, 58.2; H, 6.5; N, 5.78, 5.67.

A third portion (0.1 g.) was oxidized with nitric acid according to the method of Kiliani,[20] that is, by treatment with nitric acid (1.4 d.) for 24 hr. at 35°, for 24 hr. at 45°, and then for 24 hr. at 50°. The reaction product was diluted with water, and, after standing for 12 hr., the mixture was filtered. The filtrate was concentrated under reduced pressure at 35–40° and purified by paper chromatography with irrigant B. A chromatographically pure sirup was obtained (53 mg.) which had R_{ga}[16] and R_1[17] values of 2.9 and 1.2, respectively, in irrigant B and a $[\alpha]^{25}D$ −0.3° (*c* 2.7, water). This sirup had chromatographic flow rates in irrigants B, C and D which were identical to those of the nitric acid oxidation product of α-D-isosaccharinic acid.

Oxidation of α-D-Isosaccharinic Acid.—Calcium α-D-isosaccharinate (3.5 g.) was oxidized with nitric acid by Kiliani's method.[20] The oxidized product was isolated by paper chromatography with irrigant B; R_{ga}[16] and R_1[17] values of the product in irrigant B were, respectively, 2.9 and 1.2. The yield was 0.74 g. of sirup which contained 1.2×10^{-3} acid equivalents per gram and had $[\alpha]^{25}D$ +1.2° (*c* 7.4, water). This acid is 2-C-carboxy-3-deoxy-D-*glycero*-pentaric acid.

3-Deoxy-2-C-hydroxymethyl-D-*erythro*(or D-*threo*)-pentaric Acid (II).—The cold-water-soluble brucine salt from the above resolution was converted to the free acid by stirring its solution with Amberlite IR-120(H). When this acidic solution was concentrated under reduced pressure at 35–40°, a sirup was obtained which was purified by paper chromatography. The final sirup (0.325 g.) moved as a single component with irrigants B, C and D and had R_{ga}[16] and R_1[17] values of 3.1–3.4 and 1.2–1.3, respectively, with irrigant B. It contained 2.0×10^{-3} acid equivalents per gram and had $[\alpha]^{25}D$ +3.0° (*c* 1.3, water).

A portion of the sirup was converted to its brucine salt which, when crystallized from ethanol and placed in a capillary, began to melt at 162° and decomposed at about 250°.

Anal. Calcd. for $C_{52}H_{62}O_{15}N_4$: C, 63.6; H, 6.4; N, 5.7. Found: C, 61.7; H, 6.4; N, 5.28, 5.53.

Another portion (0.1 g.) was oxidized with nitric acid by the method of Kiliani[20] and purified chromatographically with irrigant B. A sirup was obtained which had a R_{ga}[16] value of 2.8 and a R_1[17] value of 1.2 with irrigant B and a $[\alpha]^{25}D$ +1.2° (*c* 4.3, water). This acid had chromatographic flow rates with irrigants B, C and D which were identical to those of 2-C-carboxy-3-deoxy-D-*glycero*-pentaric acid produced by nitric acid oxidation of α-D-isosaccharinic acid.

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LAFAYETTE, IND.

(16) R_{ga} is the rate of movement relative to that of D-gluconic acid.

(17) R_1 is the rate of movement relative to that of D-glucono-1,4-lactone.

(18) J. C. Sowden, Mary G. Blair and Dorothy J. Kuenne, THIS JOURNAL, **79**, 6450 (1957).

(19) R. E. Reeves, *ibid.*, **63**, 1476 (1941).

(20) H. Kiliani, *Ber.*, **18**, 631 (1885).

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Reactions of Amines. V. Synthesis of α-Amino Ketones[1,2]

BY HENRY E. BAUMGARTEN AND JAMES M. PETERSEN

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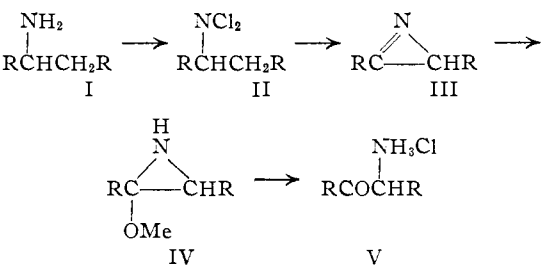
The treatment of *sec*-alkyl amines (I) with *t*-butyl hypochlorite in benzene solution followed by successive treatments of the unisolated intermediates II–IV with sodium methoxide and with dilute hydrochloric acid gave good yields of the corresponding α-amino ketone hydrochlorides V. The infrared spectra of the α-amino ketone hydrochlorides resembled to some extent the spectra of α-amino acid hydrochlorides.

In the first paper[3] of this series a new rearrangement of N,N-dichloro *sec*-alkyl amines II, which led to the formation of the corresponding α-amino ketone hydrochlorides V, was described. The present communication reports an improved procedure for the conversion of *sec*-alkyl amines I to α-amino ketone hydrochlorides *via* II and offers some measure of the scope of the reaction.

(1) Paper IV, THIS JOURNAL, **81**, 2132 (1959).

(2) This work was supported in part by grant G-3689 of the National Science Foundation.

(3) H. E. Baumgarten and F. A. Bower, THIS JOURNAL, **76**, 4561 (1954).



In the original work the amine was converted into the N,N-dichloroamine II using aqueous

TABLE I

SYNTHESIS OF α-AMINO KETONE HYDROCHLORIDES

Starting amine	Product, hydrochloride of	Reaction time,[a] min.	Yield,[b] %	M.p.,[c] °C.
Cyclopentyl	2-Aminocyclopentanone	180	36	146–147[d]
Cyclohexyl	2-Aminocyclohexanone	25–45	72[e]	156[f]
2-Aminoheptane	3-Amino-2-heptanone	210	72[g]	134–135[h]
α-Phenylethyl	Phenacylamine	70	78[i]	186.5[j]
α-(*p*-Bromophenyl)-ethyl	*p*-Bromophenacylamine	55	72.5	275[k]
α-(*p*-Chlorophenyl)-ethyl	*p*-Chlorophenacylamine	80–90	60	270–271[l]
α-(*p*-Anisyl)-ethyl	*p*-Methoxyphenacylamine	270	73.5	200[m]
α-(*p*-Nitrophenyl)-ethyl	*p*-Nitrophenacylamine	60	56	243[n]
α-(*p*-Tolyl)-ethyl	*p*-Methylphenacylamine	80–90	72	206–207[o]
α-(*p*-Xenyl)-ethyl	*p*-Phenylphenacylamine	80	71	185–186[p]
1,2,3,4-Tetrahydro-1-naphthyl	2-Amino-1-tetralone	100	69.5	201–202[q]
1,2-Diphenylethyl	Desylamine	30	45	233–234[r]

[a] See Experimental section. [b] Yield cited was maximum obtained; usual spread in yields was 5–10%. [c] All compounds melted with decomposition. [d] *Anal.* Calcd. for $C_5H_{10}ClNO$: C, 44.28; H, 7.43; N, 10.33. Found: C, 44.60; H, 7.51; N, 10.39. [e] Yield using HOCl, 42%; without special drying of reagents, 35–40%. [f] Lit.[3] m.p. 157–158°. [g] Yield using HOCl, 32%; without special drying of reagents, 65%. [h] Lit.[10] m.p. 133–134°; mixed m.p. with 1-amino-2-heptanone hydrochloride,[11] 106–110°. *Anal.* Calcd. for $C_7H_{16}ClNO$: C, 50.75; H, 9.73; N, 8.46. Found: C, 51.00; H, 9.71; N, 8.38. [i] Yield using HOCl, 52%; without special drying of reagents, 66%. [j] Lit.[3] m.p. 184–186°. [k] Lit. m.p. 258–259°,[12] 278–281°.[13] Recrystallized from 2 *N* hydrochloric acid (50 ml./g.). [l] Lit. m.p. 252°,[14] *ca.* 260°,[12] 275°,[15] 290°.[16] Recrystallized from ethanol–hydrochloric acid (150 ml./g.). [m] Lit. m.p. 197°,[17] 204°[18–20]; recrystallized from ethanol–hydrochloric acid (25 ml./g.). [n] Lit.[21] m.p. 250°; recrystallized from methanol–hydrochloric acid. [o] Lit. m.p. 206°,[17,22] 220°.[23] [p] Recrystallized from 2 *N* hydrochloric acid (150 ml./g.). *Anal.* Calcd. for $C_{14}H_{14}NOCl$: C, 67.88; H, 5.70; N, 5.66. Found: C, 67.81; H, 5.85; N, 5.81. [q] Lit.[24] m.p. 117°; product somewhat hygroscopic and tended to crystallize with one mole of water, m.p. 199–200°. *Anal.* Calcd. for $C_{10}H_{14}NO_2Cl$: C, 55.68; H, 6.54; N, 6.50. Found: C, 55.95, 55.61; H, 6.63, 6.34; N, 6.46, 6.62. Anhydrous material was obtained by drying *in vacuo* over phosphorus pentoxide at room temperature for 48 hr. *Anal.* Calcd. for $C_{10}H_{12}NOCl$: C, 60.75; H, 6.12; N, 7.09. Found: C, 60.81, 60.03; H, 6.12, 6.15; N, 7.56, 7.22. [r] Lit. m.p. 232–235°,[25] 234°.[26]

hypochlorous acid as the chlorinating agent and the intermediate II was isolated prior to the rearrangement steps. Among the other halogenating agents[4–8] that have been used for the preparation of N-halo amines, *t*-butyl hypochlorite appeared to be especially promising, for Bachman, Cava and Dreiding[8] had shown that the monochlorination of the N-chloro amine and hydrolysis of the resultant imine to the corresponding aldehyde or ketone could be carried out conveniently without isolating the chloro amine.

A series of exploratory experiments with α-phenylethylamine in which *t*-butyl hypochlorite was used as a halogenating agent showed that, when benzene was used as a solvent and subsequent reactions (II → V) were carried out on the benzene solution, a 68% yield of phenacylamine hydrochloride could be obtained. Substitution of the lower-boiling solvents, ether or Skellysolve B, for benzene resulted in an extended reaction time and a much lower yield (33%). Careful drying of the reactants and apparatus permitted a further increase in the yield of phenacylamine hydrochloride to 78% and gave a more nearly pure product. The latter observations are in accordance with those made earlier[3] and with the recent experiments of Smith and Most[9] on the rearrangement of dimethylhydrazone methiodides, which gave good yield of amino ketone only in the absence of water.

In Table I are given a number of examples of the synthesis of α-amino ketone hydrochlorides from *sec*-alkyl amines *via* the N,N-dichloramine. In a few of the examples both the hypochlorous acid and the *t*-butyl hypochlorite techniques were employed, and in all cases the latter was superior. The beneficial effect of maintaining anhydrous conditions is also indicated by the results in Table I. Very good yields of the amino ketone hydrochlorides were obtained in nearly all instances, that of 2-aminocyclopentanone being considerably lower than the rest. The reaction in this instance was not nearly as clean as in the other examples and the product was more difficult to purify. Possibly this result can be correlated with the

(4) S. W. Fox and M. W. Bullock, THIS JOURNAL, **73**, 2754 (1951): chloramine T.

(5) S. Goldschmidt, R. Endres and R. Dirsch, *Ber.*, **58**, 573 (1925): ethyl hypochlorite.

(6) A. Schönberg, R. Moubasher and M. Z. Barakat, *J. Chem. Soc.*, 2504 (1951): N-bromosuccinimide, N-bromophthalimide.

(7) T. Seliwanow, *Ber.*, **26**, 426 (1893): N-haloacetamides.

(8) W. E. Bachmann, M. P. Cava and A. S. Dreiding, THIS JOURNAL, **76**, 5554 (1954).

(9) P. A. S. Smith and E. E. Most, *J. Org. Chem.*, **22**, 358 (1957).

(10) F. E. Lehmann, A. Bretscher, H. Kuhne, E. Sarkin, M. Erne and H. Erlenmeyer, *Helv. Chim. Acta*, **33**, 1217 (1950).

(11) We are indebted to Dr. A. W. Schrecker for providing us with an authentic sample of 1-amine-2-heptanone hydrochloride (m.p. 166.5–168° dec.

(12) N. P. Buu-Hoi, N. Hoan, P. Jacquignon and H. H. Khoi, *Compt. rend.*, **230**, 662 (1950).

(13) L. L. Bambas, H. D. Troutman and L. M. Long, THIS JOURNAL, **72**, 4445 (1950).

(14) A. B. Sen and D. D. Mukerji, *J. Indian Chem. Soc.*, **28**, 401 (1951).

(15) O. Danns, H. Ulrich and E. Moller, *Z. Naturforsch.*, **7b**, 344 (1952).

(16) R. P. Edkins and W. H. Linnell, *Quart. J. Pharm. Pharmacol.*, **9**, 75 (1936).

(17) B. Reichert and H. Baege, *Pharmazie*, **2**, 451 (1947).

(18) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1547 (1911).

(19) H. D. Moed, M. Asscher, P. J. A. Van Draanen and H. Hiewind, *Rec. trav. chim.*, **71**, 933 (1952).

(20) F. Tutin, *J. Chem. Soc.*, **97**, 2509 (1910).

(21) L. M. Long and N. D. Troutman, THIS JOURNAL, **75**, 38 (1953).

(22) H. Ryan, *Ber.*, **31**, 2129 (1898).

(23) N. P. Buu-Hoi, N. D. Xuong and H. H. Khoi, *J. Chem. Soc.*, 255 (1951).

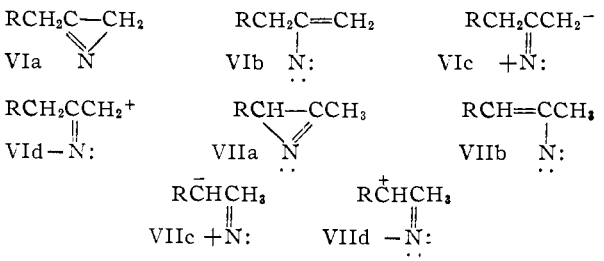
(24) P. W. Neber, A. Burgard and W. Thier, *Ann.*, **526**, 277 (1936).

(25) M. S. Hatch and D. J. Cram, THIS JOURNAL, **75**, 38 (1953).

(26) P. W. Neber and G. Huh, *Ann.*, **515**, 283 (1935).

smaller ring size and the resultant instability of the fused 3-ring-5-ring intermediate IV.

It is interesting to note that the product (or at least the predominating product) from 2-aminoheptane was 3-amino-2-heptanone hydrochloride[10] rather than 1-amino-2-heptanone hydrochloride.[11] The assignment of structure was based upon a comparison of the product from the present synthesis with authentic samples of the two amino ketone hydrochlorides, both with respect to melting points and infrared spectra. This result may be rationalized by assuming that the transition state for the second dehydrohalogenation step occurs sufficiently far along the reaction coördinate so that it resembles the products, VIa or VIIa, methanol and chloride ion. Of the two azirine intermediates, the intermediate with the larger number of alkyl substituents, VIIa, would be expected to be the more stable, if, indeed, either is capable of existence. Hatch and Cram[25] have suggested representations such as VIb ↔ VIc ↔ VId and VIIb ↔ VIIc ↔ VIId as being more plausible and in keeping with the apparent absence of stereospecificity in a similar elimination, the Neber rearrangement. Presumably the more highly substituted VIIb would be more stable than VIb and VIId should receive more inductive or hyperconjugative stabilization than VId, so that the species VII as a whole should be more stable than VI.



The results obtained with the *p*-substituted α-phenylethylamines indicate that the reaction is not especially sensitive to the type of substitution on the aromatic ring. The lowest yield in this series was 56% for α-(*p*-nitrophenyl)-ethylamine, the lower yield apparently being caused by a greater incidence of side reactions. From the time required for the disappearance of active halogen from the reaction mixture, it appears that the *p*-nitro derivative reacted most rapidly and the *p*-methoxy least rapidly, a result that is in agreement with the suggested mechanism for the reaction,[3] inasmuch as an electron-withdrawing *p*-substituent should facilitate both the removal of the α-proton in the first stage of the reaction and the β-proton in the second.

As part of their evidence for the occurrence of intermediates like IV in the Neber rearrangement, Hatch and Cram[25] showed that reduction with lithium aluminum hydride of a supposed intermediate obtained from the rearrangement of the tosylate of the oxime of deoxybenzoin gave *cis*-2,3-diphenylethyleneimine. In the present work the similar reduction of an intermediate (IV, R = C_6H_5) obtained from the rearrangement of N,N-dichloro-1,2-diphenylethylamine (II, R = C_6H_5) gave *cis*-2,3-diphenylethyleneimine in 43% yield. This result lends further support to the suggested mechanism for the reaction.[3] Furthermore, this preparation represents a new synthesis of ethyleneimines.

The preparation of *p*-nitrophenacylamine hydrochloride represents in effect another route to a key intermediate in the synthesis of chloramphenicol.[21] The starting amine may be readily prepared from α-phenylethylamine by acetylation of the amine, nitration of the resultant N-(*p*-nitrophenylethyl)-acetamide and hydrolysis of the amide.[27] Although this route is relatively simple, the over-all yield for the several steps required (28%) appears to be somewhat lower than that obtained by other routes.[21]

In Table II are given selected values from the infrared spectra of the α-amino ketones hydrochlorides prepared. As might be expected the spectra of these compounds show a rather close resemblance to the spectra of α-amino acid hydrochlorides.[28] No absorption in the usual N–H stretching region (3300–3500 cm.$^{-1}$) was shown by any of the products. However, a broad band appears near 3000 cm.$^{-1}$ which may be assigned to the $-NH_3^+$ stretching mode. An almost continuous series of band appeared between 3000 and 2400 cm.$^{-1}$, similar to the bands shown by amino acid hydrochlorides. The band near 2000 cm.$^{-1}$ found in the spectra of the $-NH_3^+$ type of amino acid hydrochlorides was also present in the spectra of the amino ketone hydrochlorides. In the 1500–1600 cm.$^{-1}$ region two bands were observed in addition to any bands assigned to aromatic ring vibrations. Presumably these may be correlated with the $-NH_3^+$ deformation bands, since they fall in the same region as the corresponding bands for the amino acid hydrochlorides. The position of the absorption band of the carbonyl group was in general fairly close to that of the parent ketone. Because of differences in state, the present spectra being determined using mulls or potassium bromide pellets, the origin of any frequency shifts of this band cannot be determined. However, most of the carbonyl absorption bands did occur at a slightly higher frequency than those for the corresponding parent ketones. This slight elevation of the frequency may reflect the influence of the $-NH_3^+$ group on the C=O link of the adjacent carbonyl group.

Experimental[29]

Reagent grade benzene was dried by distillation, discarding the first 10% of the distillate. Commercial absolute methanol was dried by refluxing over magnesium turnings (1 g./100 ml. of methanol) for four hours and distilling into oven-dried receivers. *dl*-α-Phenylethylamine (Matheson, Coleman, Bell and Co.) was used without further treatment. Cyclohexylamine (Eastman Kodak Co.) was redistilled and stored over potassium hydroxide pellets. 2-Aminoheptane (K and K Chemical Co.) was stored over potassium hydroxide pellets.

***p*-Substituted α-Phenylethylamines.**—All of the *p*-substituted α-phenylethylamines except the *p*-nitro derivative were prepared by the Leuckart procedure using the experi-

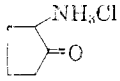
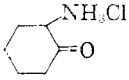
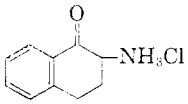
(27) H. Reihlen and E. Hezel, *Ann.*, **487**, 213 (1931).

(28) R. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 200.

(29) Melting points are corrected; boiling points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

TABLE II

INFRARED SPECTRA[a]

Compound	(NH) region	2000-cm.$^{-1}$ region	(C=O) region	1500–1600-cm.$^{-1}$ region	Parent ketone (C=O)
$CH_3(CH_2)_4COCH_2NH_3Cl$	2940	1940	1717	1597bb, 1505s, 1472s	1718, 1720 (liq.)[c,d]
$CH_3(CH_2)_3CHCOCH_3$ (NH$_3$Cl) [b]	2960	1990	1718	1603w, 1575w, 1477s	
NH_3Cl	2950	1990	1720	1605w, 1578w, 1482s	
	2930	1998	1748	1607w, 1599sh, 1565w, 1500m	1744 (liq.)[a]
	2870	2035	1716	1585sh, 1578w, 1503m	1714 (liq.)[d]
	2930	2000	1686	1601m, 1580sh, 1512sh, 1495m	1679 (liq.)[e]
$C_6H_5COCH_2NH_3Cl$	2870	1985	1691	1610w, 1595sh, 1580sh, 1530s, 1492m	1687 (liq.)[f]
p-$BrC_6H_4COCH_2NH_3Cl$	2970	2020	1677	1603w, 1586w, 1568sh, 1472s	1663 (Nuj.)[g]
p-$ClC_6H_4COCH_2NH_3Cl$	2910	2020	1678	1591s, 1582sh, 1573sh, 1563sh, 1473s	1686 (liq.)[g]
p-$CH_3OC_6H_4COCH_2NH_3Cl$	2905	1987	1676	1602m, 1575sh, 1512sh, 1503m	1658 (Nuj.)[g]
p-$NO_2C_6H_4COCH_2NH_3Cl$	3020	1960	1683	1604m, 1597sh, 1580sh, 1530s, 1492m	1686 (Nug.)[g]
p-$CH_3C_6H_4COCH_2NH_3Cl$	2910	2010	1680	1607m, 1577m, 1473s	1673 (liq.)[g]
p-$C_6H_5C_6H_4COCH_2NH_3Cl$	2935	1940	1678	1603m, 1580sh, 1563sh, 1514sh, 1489m	1679 (KBr)

[a] Infrared measurements were made with a Perkin–Elmer model 21 double-beam instrument fitted with sodium chloride optics and using potassium bromide wafers. [b] First value is for compound prepared from the N,N-dichloroamine, second for compound prepared by Dakin-West procedure.[10] [c] J. Lascombe and M. L. Josien, *Bull. soc. chim. France*, 1227 (1955). [d] E. J. Hartwell, R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1436 (1948). [e] A. Hassner and N. H. Cromwell, THIS JOURNAL, **80**, 893 (1958). [f] H. L. Hergert and E. F. Kurth, *ibid.*, **75**, 1622 (1953). [g] A. H. Soloway and S. L. Friess, *ibid.*, **73**, 5000 (1951).

mental procedure reported for α-(p-chlorophenyl)-ethylamine[30] with the exception that ammonium formate and formic acid were used as reactants instead of formamide and formic acid. The only other deviation in procedure was in the case of α-(p-xenyl)-ethylamine in which the formyl derivative was isolated by pouring into cold water rather than by extraction with benzene. Yields were close to those reported by Ingersoll, Brown, Kim, Beaucamp and Jennings[31] except for the p-methoxy derivative which was obtained in only 26% yield. Although these workers were unable to distil α-(p-xenyl)-ethylamine satisfactorily at 10 mm., we found it to distil quite readily at 142–142.5° (1.8 mm.).

1,2,3,4-Tetrahydro-1-naphthylamine.—The Leuckart reaction was used to prepare this amine according to the procedure cited above. From 0.5 mole of 1-tetralone, 31.5 g. (43%) of 1,2,3,4-tetrahydro-1-naphthylamine, b.p. 120° (12 mm.) (lit.[32] b.p. 114° (10 mm.)), was obtained.

α-(p-Nitrophenyl)-ethylamine.—The following procedure gave somewhat better results than those reported by Reihlen and Hezel[27] and gives details omitted by them.

To a solution of 67 g. (0.40 mole) of crude N-acetyl-α-phenylethylamine in 56 ml. of glacial acetic acid was added 80 ml. of concentrated sulfuric acid, with intermittent cooling such as to maintain the temperature below 25°. The resultant solution was cooled to 5° and a mixture of 38 g. (26 ml., 0.60 mole) of concentrated nitric acid and 37 ml. of concentrated sulfuric acid was added dropwise while maintaining the temperature below 15°. After addition of the nitrating mixture was complete, the reaction mixture was stirred at room temperature for 4.5 hr. The stirring time was somewhat critical for, when the time was less than that specified, or when the reaction mixture was stirred overnight at room temperature, the yield was greatly reduced. The reaction mixture was poured with rapid stirring into a mixture of 800 ml. of water and 400 g. of ice. The crude N-acetyl-α-(p-nitrophenyl)-ethylamine was collected by filtration and used in the next step without drying. In one run the crude product was air-dried and found to weigh 80 g. (96%). Neutralization of the acidic reaction mixture did not yield further product.

The crude, moist N-acetyl-α-(p-nitrophenyl)-ethylamine was dissolved in 480 ml. of 20% hydrochloric acid solution and heated under reflux for 4 hours. From the cooled reaction mixture the crude amine hydrochloride was collected (61 g., 76%) by filtration. The salt was dissolved in water and the free base was liberated by addition of 33% potassium hydroxide solution to the chilled solution. The resulting oil was extracted with ether. The ethereal extract was dried over magnesium sulfate, filtered and distilled under reduced pressure, giving 25 g. (50%) of α-(p-nitrophenyl)-ethylamine, b.p. 135–138° (2.5 mm.) (lit.[27] b.p. 162° (14 mm.), 100° (high vacuum)).

1,2-Diphenylethylamine.—This amine was prepared by the Leuckart reaction according to the procedure cited above, the crude formyl derivative being isolated by pouring the reaction mixture into cold water. From 0.88 mole of deoxybenzoin, 134 g. (78%) of 1,2-diphenylethylamine, b.p. 142–143° (2.9 mm.), was obtained.

α-Amino Ketone Hydrochlorides (V).—Virtually the same procedure was used for the preparation of all the α-amino ketone hydrochlorides listed in Table I. The specific procedure for the preparation of phenacylamine hydrochloride is given, and any deviations from this procedure for the other amino ketone hydrochlorides are given after the procedure. All glassware was dried by baking in the oven (120–140°) and whenever possible solvents were distilled directly into the reaction vessel to be used. Many experiments were carried out to determine the optimum amounts of reagents, order of addition of reactants and reaction times, and the following procedure was based on the results of these experiments.

To a solution of 12.1 g. (13.0 ml., 0.10 mole) of α-phenylethylamine in 50 ml. of anhydrous benzene in a 3-necked flask, fitted with a mechanical stirrer, dropping funnel and Y-tube containing a thermometer and calcium chloride tube and cooled in an ice–salt-bath, was added dropwise with stirring a solution of 21.7 g. (27.5 ml., 0.22 mole) of t-butyl hypochlorite[33] in 50 ml. of anhydrous benzene at such a rate as to maintain the temperature below 10°. After the addi-

(30) M. L. Moore, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 321.

(31) A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beaucamp and G. Jennings, THIS JOURNAL, **58**, 1808 (1936).

(32) W. Davis, J. L. Everett and J. C. J. Ross, *J. Chem. Soc.*, 1331 (1950).

(33) H. M. Teeter and E. W. Bell, *Org. Syntheses*, **32**, 20 (1952)

tion was complete the ice–salt-bath was removed and the reaction mixture was stirred for 1–4 hr. at room temperature.

The thermometer was replaced by a condenser and a solution of 7.0 g. (0.3 g. atom) of sodium in 70 ml. of absolute methanol (dried over magnesium methoxide) was added dropwise at such a rate as to maintain gentle reflux. After the addition was complete the reflux was maintained by external heating to complete the reaction. The reaction was considered complete when a test portion of the reaction mixture gave a negative test with acidified starch–iodide paper (70 min.). The reaction mixture was cooled, and the precipitated sodium chloride was removed by filtration and washed three times with small portions of dry benzene. The filtrate was poured cautiously *into* a separatory funnel containing 150 ml. of 2 *N* hydrochloric acid solution.[34] The aqueous portion was separated and the benzene layer was extracted three times with 50-ml. portions of 2 *N* hydrochloric acid solution. The combined acid extracts were washed twice with 50-ml. portions of ether (which were discarded).

The aqueous solution was evaporated to dryness in a rotating evaporator at a temperature below 40°. The residue was extracted (under reflux) with 200-ml. and 150-ml. portions of isopropyl alcohol to which 1.0 ml. of concentrated hydrochloric acid per 100 ml. of alcohol had been added.[35] The precipitate which formed upon cooling the extracts separately was removed by filtration and washed with dry ether. The filtrates were either evaporated under reduced pressure to approximately half of their original volumes or were diluted with equal volumes of ether. Either treatment yielded a second crop of crystals (also washed with ether). The total yield of phenacylamine hydrochloride was 13.4 g. (78%), m.p. 186.6° dec.

The principal variations necessary in the preparations of the other amino ketone hydrochlorides were as follows. In the preparation of *p*-nitrophenacylamine hydrochloride the addition of the sodium methoxide solution was carried out in an ice–water-bath to maintain the temperature below 10°. Even so the color of the solution changed from yellow to green to brown as the addition progressed. After the addition was complete the mixture was stirred at room temperature until a negative test was obtained with starch–iodide paper (2 hours) or, less desirably, heated on the steam-bath (60 min.). The times required to obtain a negative test with starch–iodide paper for the other preparations are listed in Table I as reaction times. In the preparation of 2-amino cyclopentanone the aqueous acid extract was quite dark and was treated three times with charcoal before evaporation. Both this product and 2-aminocyclohexanone had limited shelf lives, but they could be kept up to several months.

Normally the benzene extracts were discarded after treatment with the aqueous acids. In the preparation of desylamine hydrochloride, however, the benzene was evaporated. The yellow-orange oil that remained deposited yellow crystals which were recrystallized from Skellysolve B yielding 200 mg. of yellow needles, m.p. 84–85°. This material was identified as benzil by determination of mixture m.p.'s and infrared spectrum.

cis-2,3-Diphenylethyleneimine.—Starting with 4.9 g. (0.025 mole) of 1,2-diphenylethylamine and proportionate quantities of other reagents, the procedure described above for the preparation of α-amino ketones was followed to the point at which a negative test for positive halogen was obtained with starch–iodide paper. The reaction mixture was cooled and the precipitated sodium chloride was removed by filtration and washed twice with small portions of dry benzene. The combined benzene solutions were poured with stirring into 150 ml. of ice-water. The benzene layer was separated and diluted with an equal volume of ether. The benzene–ether mixture was cooled in an acetone–Dry Ice-bath. After the benzene had crystallized, it was filtered off rapidly through a thoroughly chilled Buchner funnel. The essentially ethereal filtrate was dried over magnesium sulfate for 30 minutes.

To a slurry of 4.0 g. (0.1 mole) of lithium aluminum hydride in 1200 ml. of dry ether the above ethereal solution was added dropwise with stirring. After addition was complete, the reaction mixture was stirred at room temperature for 20 min. To the mixture the following were added dropwise: 4 ml. of water, 4 ml. of 15% sodium hydroxide and 12 ml. of water. The precipitate was removed by filtration and the ethereal solution was dried over magnesium sulfate. Evaporation of the ether gave 2.5 g. of yellow solid, which on recrystallization from 10 ml. of Skellysolve B yielded 2.0 g. (43%) of *cis*-2,3-diphenylethyleneimine, m.p. 82–84° (lit.[25] m.p. 81–82.5°). Repeated recrystallization from Skellysolve B raised the m.p. to 84–85°. The infrared spectrum of the product was nearly identical with that reported by Hatch and Cram.[25]

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(34) The reverse order of addition may lead to the formation of the self condensation products of the α-amino ketone.

(35) Inasmuch as sodium chloride is very nearly insoluble in hot isopropyl alcohol, the latter is the solvent of choice for such extractions. For less soluble amino ketone hydrochlorides, ethyl or methyl alcohols could be used, but the products may have been contaminated with traces of sodium chloride.

[CONTRIBUTION FROM THE KETTERING–MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XX. 2-Fluoropurines[2]

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The 2-fluoro derivatives of a number of biologically active purines have been prepared from the corresponding 2-aminopurines by a modified Schiemann reaction. The properties of these compounds are discussed.

Many organic fluorine compounds have shown interesting biological activity. An excellent review of fluorine-containing drugs was published in 1954.[3] Since that time, a large number of such compounds have appeared in the literature; for example, fluorobarbiturates,[4] fluoroacetylcholine,[5] fluoro-anesthetics,[6] 9α-fluorohydrocortisone,[7] Vesprin,[8] and some potential anticancer agents (fluorourethans[9] and fluoroaromatics[10]). More recently, several 5-fluoropyrimidines[11] showing marked tumor-inhibiting properties[12] and some trifluoromethylpurines[13] have been prepared.

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(2) For paper XIX of this series, see J. A. Montgomery, L. B. Holum and T. P. Johnston, THIS JOURNAL, **81**, 3963 (1959).

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