presence of a small amount of Δ^{16}-20-acetoxy material may account, in part, for the difficulties encountered in obtaining crystalline material.

A similar acid-catalyzed equilibration of a 1:1 mixture of 20α- and 20β-hydroxy-Δ^{16}-3-ethylene ketals[10] afforded the same mixture of products in the same relative proportions as were isolated from the pure 20α isomer.

16α-Hydroxy-4,17(20)-(*trans*)-pregnadien-3-one (13a).—The treatment of the 16α-acetate **13b** with alcoholic potassium hydroxide at reflux for 1.5 hr. afforded the 16α-hydroxy compound (**13a**). The product crystallized as needles from ether–petroleum ether (b.p. 66–69°) and had m.p. 173.5–175.5°; $[\alpha]_D$ +104.5°; ΔM_D (16-OAc–16-OH) −311°; λ_{max} 240 mμ (ϵ 16,700); $\Delta\nu$ 47.5 (18-H), 72.5 (19-H), 105, 112 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.21; H, 9.54.

16β-Hydroxy-4,17(20)-(*trans*)-pregnadien-3-one (12a).—Alkaline hydrolysis of the 16β-acetate (**12b**) afforded the 16β-hydroxy compound (**12a**) as blades from ether–petroleum ether, m.p. 172–175°; $[\alpha]_D$ +141.5°; ΔM_D (16-OAc–16-OH) −39°; λ_{max} 240.5 mμ (ϵ 16,850); $\Delta\nu$ 58.4 (18-H), 72.2 (19-H) 100, 106 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.55; H, 9.70.

Preparation of Amino Acids from Trichloromethylcarbinols[1]

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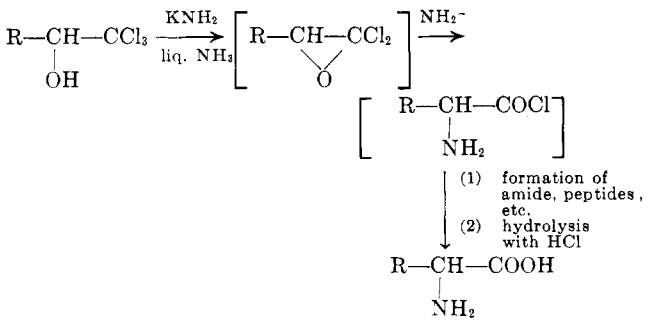
The conversion of four trichloromethylcarbinols to amino acids by treatment with potassium amide in liquid ammonia at −33° has been studied. The reaction occurs in 29 to 48% yields, and is believed to involve the formation of an intermediate epoxide followed by the opening of the epoxide ring by amide ion. The amino acids prepared were α-aminobutyric acid, valine, 2-methyl-2-aminopropionic acid, and phenylglycine. Methods of preparing alkyl and aryl trichloromethylcarbinols are reviewed and discussed.

Alkyl and aryl trichloromethylcarbinols are potentially useful intermediates for the synthesis of α-substituted carboxylic acids. It is known that phenyltrichloromethylcarbinol reacts with a concentrated aqueous potassium hydroxide solution to form α-chlorophenylacetic acid in 26% yield,[3] with methanolic potassium hydroxide to form α-methoxyphenylacetic acid in 72% yield,[4] and with ethanolic sodium ethoxide to form α-ethoxyphenylacetic acid in 33% yield.[5] The mechanism proposed for these reactions involves the intermediate formation of an epoxide and the subsequent opening of the epoxide ring by a nucleophilic reagent.[6] In the present work, amide ion was used as the nucleophilic reagent to obtain α-amino acids.



The conversion of four trichloromethylcarbinols to amino acids was studied (Table I). The R group in the above equation was ethyl, isopropyl, and phenyl. In addition, 1,1,1-trichloro-2-methyl-2-propanol (chlorobutanol) was studied. In all cases, the reaction was carried out by adding the carbinol to a solution of potassium amide in liquid ammonia at −33°. The mixture was stirred for 8 to 12 hr. the ammonia was allowed to evaporate, and the final amino acid was obtained by hydrolyzing the initially formed products with ethanolic hydrochloric acid.

Attempts were made to isolate the α-amino amide, a postulated intermediate prior to acid hydrolysis, but positive identification could not be made. It appears that a mixture of products are formed at this stage of the reaction. Thus, if the excess potassium amide is decomposed under mild conditions, *e.g.*, by the use of 95% ethanol, and the hydrolysis step with hydrochloric acid is omitted, phenylglycine is still obtained in 5 to 12% yield. When hydrolyzed with hydrochloric acid, the yield is 48%. Apparently, there are both readily hydrolyzable and difficultly hydrolyzable species in the reaction mixture. The former probably includes the amino acid amide; the latter may include the diketopiperazine, peptides, and Schiff bases. Even under what appeared to be optimum conditions, a red, viscous nonhydrolyzable oil accounted for about half of the reaction product. Infrared spectroscopy and v.p.c. showed benzaldehyde and unchanged starting materials to be two of the major components of this oil.

Optimum reaction conditions were determined with phenyltrichloromethylcarbinol. With potassium amide the reaction did occur, whereas sodamide was ineffective, presumably because of its insolubility in the liquid ammonia solvent. Even powdered potassium hydroxide slurried in liquid ammonia was almost as effective (39% yield) as the potassium amide. With no base present there was no reaction. Using potassium hydroxide as the base, attempts to carry out the reaction at 30 and at 100° in a steel hydrogenation vessel gave only 15% yields, probably because the rocking autoclave provided insufficient agitation. The reaction was also carried out at 48° in a methanolic potassium hydroxide solution saturated with ammonia, and a 34% yield of phenylglycine was obtained.

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(2) This investigation was supported in part by a Predoctoral Fellowship to L. W. F. from the Division of General Medical Studies, U. S. Public Health Service.

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TABLE I

PREPARATION OF α-AMINO ACIDS FROM TRICHLOROMETHYLCARBINOLS

Amino acid (yield, g.)	Carbinol (g.)	Yield, %[a]	M.p., °C. dec.[a]	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
α-Aminobutyric (3.0)	$C_2H_5CHOHCCl_3$ (18)	29	268[b]	46.59	46.60	8.79	8.54	13.59	13.32
Valine (3.9)	$(CH_3)_2CHCHOHCCl_3$ (19)	34[c]	292–295[d]	51.25	51.40	9.48	9.75	11.95	12.15
2-Methyl-2-aminopropionic (4.5)	$CH_3C(CH_3)OHCCl_3$ (18)	43	280[e]	46.59	46.59	8.79	8.50	13.59	13.41
Phenylglycine (7.3)	$C_6H_5CHOHCCl_3$ (22)	48	253–256[b]	63.56	63.46	6.00	6.28	9.26	9.01

[a] After amino acids were recrystallized from water. [b] N. Zelinski and G. Stadnikoff, *Ber.*, **41**, 2061 (1908). [c] Potassium amide prepared by method of P. A. McCuster and R. R. Vogt [*J. Am. Chem. Soc.*, **59**, 1307 (1937)]. [d] M. D. Slimmer [*Ber.*, **35**, 400 (1902)] reports m.p. 295–299° dec. [e] N. Zelinski and G. Stadnikoff, *ibid.*, **39**, 1726 (1906).

Formation of the Trichloromethylcarbinols.—The practical utility of the reaction for preparing amino acids depends very much on the ready availability of the starting trichloromethylcarbinols. The aryl trichloromethylcarbinols are readily available by any of the following three methods. First, reaction of aromatic aldehydes with chloroform at 0° in the presence of dry potassium hydroxide usually results in about 45% yields of the carbinols.[3,7] In the case of benzaldehyde and chloroform, we have increased the yield to 75% by the use of potassium *t*-butoxide in *t*-butyl alcohol. A second general method involves the normal addition of aryl Grignard reagents to chloral, usually in about 50% yield.[8] The third procedure involves the reaction of chloral with benzene, toluene, or *p*-xylene in the presence of aluminum chloride to form the trichloromethylcarbinol, usually in about 70% yield.[9]

The synthesis of alkyl trichloromethylcarbinols is much more difficult. Acetone will undergo a condensation with chloroform, catalyzed by potassium hydroxide, in 84% yield,[10] but the yields are very low when aldehydes are condensed with chloroform. In the present work, isopropyltrichloromethylcarbinol was prepared in 18% yield from isobutyraldehyde and chloroform using potassium *t*-butoxide as the base. Most alkyl Grignard reagents on reacting with chloral undergo oxidation–reduction exclusively, with formation of an olefin and trichloroethanol. Certain Grignard reagents, such as methyl- and benzylmagnesium halides, which cannot undergo this side reaction, give the normal carbinol adduct in good yield.[8] Vinyl and substituted vinylmagnesium halides also add normally to chloral in approximately 30% yield, and the trichloromethylvinylcarbinols can be hydrogenated quantitatively over a palladium-on-carbon catalyst to the alkyl trichloromethylcarbinols. The ethyltrichloromethylcarbinol used in this work was prepared in this way.[11] Unfortunately, the substituted vinyl halides are not easily obtained in good yield.

Experimental

All melting and boiling points are corrected. Analyses are by Dr. Franz J. Kasler. The infrared spectra were determined on a Beckman IR-5.

General Procedure for the Reaction of Trichloromethylcarbinols with Amide Ion.—To a 1000-ml., three-necked flask, equipped with a dropping funnel and Hershberg stirrer and placed neck-deep in a large dewar flask, was added 0.6 l. of liquid ammonia. A slice of potassium was added followed by a crystal (approximately 2 mm.[3] in size) of anhydrous ferric nitrate. The solution changed from blue to pale yellow. The rest of the potassium (total of 18 g., 0.45 g.-atom) was then added at a rate such that each piece had reacted before the next was introduced. This required about 30 min. The carbinol (0.1 mole) was then added dropwise over a period of about 10 min., and the reaction mixture was stirred for an additional 12 hr.

The ammonia was allowed to evaporate and the last traces were removed using a warm-water bath. The flask was cooled in an ice bath and 100 ml. of absolute ethyl alcohol was added in one portion; this was followed by the dropwise addition of 100 ml. of concentrated hydrochloric acid over a 15-min. period. The mixture was filtered; the filtrate was refluxed for 12 hr. and then evaporated nearly to dryness on a steam bath to remove most of the hydrochloric acid. A red oil remained. Much of this dissolved when treated with 100 ml. of water. The mixture was extracted twice with 25-ml. portions of ether and the aqueous solution was made alkaline (pH approximately 11) with a saturated lithium hydroxide solution. The mixture was again extracted with ether, treated with decolorizing carbon, filtered, and neutralized to pH approximately 6 with dilute hydrochloric acid. The solution was then concentrated to a volume of approximately 20 ml. on a steam bath. A fivefold excess of anhydrous ethanol was added and the salts which immediately precipitated were filtered off. The amino acid began to precipitate after a period varying from 30 min. (for phenylglycine) to 2 weeks (for α-aminobutyric acid and α-aminoisobutyric acid).

Phenyltrichloromethylcarbinol.—Most of this was prepared by the reaction of chloroform with benzaldehyde in the presence of dry, powdered potassium hydroxide[7] according to the following procedure. In a 1000-ml., three-necked flask, equipped with a condenser, thermometer, and an efficient Hershberg stirrer, were placed 212 g. (2 moles) of redistilled benzaldehyde and 400 g. (3.3 moles) of chloroform. The solution was cooled to 0°, and 120 g. (2.1 moles) of freshly powdered potassium hydroxide pellets were spooned in, in small portions, over a 1-hr. period. After an induction period of approximately 0.5 hr., the reaction mixture rapidly became very thick and much heat was evolved. The reaction mixture was stirred for 30 min. longer, 150 ml. of cold water was added, and the mixture was poured into a mixture of ice and excess 6 *N* sulfuric acid. On distillation, 215 g. of α-(**trichloromethyl**)**benzyl alcohol** (47% yield) was obtained, b.p. 148–149° (17 mm.), $n^{30}D$ 1.5660. The infrared spectrum showed ν_{max} (liq. film between salt plates) 3550–3300, 3050, 2925, 1500, 1485, 1455, 1390, 1335, 1300, 1230, 1200–1170, 1090, 1060, 1030, 1010, 1000, 925, 855, 835–810, 785–770, 755–735, 710–695, and 655–640 cm.$^{-1}$.

The second method for preparing phenyltrichloromethylcarbinol used potassium *t*-butoxide as the base. To a stirred solution of 32 g. (0.3 mole) of redistilled benzaldehyde in 143 g. (1.20 moles) of chloroform was added at 0° over a 45-min. period a solution prepared from 18 g. (0.45 mole) of potassium and 300 ml. of *t*-butyl alcohol. After stirring for another 45 min., 150 ml. of dry benzene was added, and the reaction mixture was stirred for 3 hr. at 0°. The reaction mixture was poured into 300 ml. of ice–water containing sufficient sulfuric acid to acidify the mixture to congo red, and was worked up as before. Distillation gave 51 g. of product (75% yield), b.p. 148–149° (17 mm.). A 15% yield of benzaldehyde was recovered as forerun.

Isopropyltrichloromethylcarbinol.—This was prepared by the potassium *t*-butoxide procedure given above. From 22 g. (0.3

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(10) C. Weizmann, E. D. Bergmann, and M. Sulzbacher, *J. Am. Chem. Soc.*, **70**, 1189 (1948).

(11) H. Normant and J. Ficini, *Bull. soc. chim. France*, 1441 (1956); W. Reeve and L. W. Fine, *J. Am. Chem. Soc.*, **86**, 880 (1964).

mole) of isobutyraldehyde, there was obtained 10 g. (18% yield) of **1,1,1-trichloro-3-methyl-2-butanol**, b.p. 88–89° (20 mm.), $n^{25}D$ 1.4737. The physical constants are in agreement with those of Normant and Ficini[11] who prepared it by another method. The infrared spectrum showed ν_{max} (liq. film between salt plates) 3575–3350, 3000, 2900, 1495, 1405, 1380, 1305, 1250, 1180, 1150, 1110, 1055, 1020, 920, 855–800, 780–750, and 660–640 cm.$^{-1}$.

Anal. Calcd. for $C_5H_9Cl_3O$: C, 31.34; H, 4.73; Cl, 55.58. Found: C, 31.58; H, 4.92; Cl, 55.30.

Using potassium hydroxide as the base, the yield was 12% of theory.

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The Thermal Decomposition of 2-Azidobenzylideneamines

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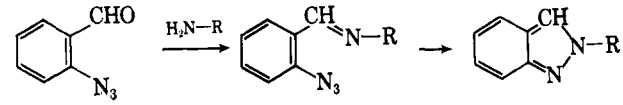
The synthesis and thermal decomposition of a series of 2-azidobenzylideneamines are described. In every case the reaction resulted in an intramolecular cyclization to yield a five-membered ring structure possessing the indazole nucleus.

Thermal- or photo-induced decompositions of biaryl azides which result in intramolecular cyclization with a loss of nitrogen are well-known. For example, Smith and co-workers[1] have reported that the decomposition of 2-azidobiphenyl produced carbazole in high yield. This reaction has been extended to vinyl azides by Smolinsky[2] who obtained 2-phenylazirine upon pyrolysis of α-azidostyrene. The decomposition of 2,2′-diazidoazobenzene has been reported by Carboni and Castle[3] to yield 1,3a,4,6a-tetraazapentalene. The decomposition of azides has been shown by several workers[4] to be capable of intramolecular cyclization at saturated centers. These products can be explained readily by a mechanism involving a univalent, uncharged nitrogen atom frequently called an azene. This intermediate also has been called nitrene, imene, and imine.

Analogous cyclization reactions proceeding presumably through the azene intermediate have also been effected by the reduction of a nitroso or nitro group. Thus, 2-nitrobenzylideneaniline[5] upon treatment with triethyl phosphite was reduced to 2-phenylindazole, and, similarly, 2-nitroso-[6] and 2-nitrobiphenyls[7] were converted to the corresponding carbazoles. The reductive cyclization of 2-nitrophenylpyridine[8] also has been reported.

In this report there are described the thermal decompositions of 2-azidobenzylideneamines in an inert solvent to yield cyclized products. The synthesis of the starting azido compounds with one exception were conveniently effected by the condensation of 2-azidobenzaldehyde with the appropriate amine. These azides are listed in Table I. The decomposition of the azide was carried out in either 1,2-dichloro- or 1,2,4-trichlorobenzene at a temperature (approximately 150°) where a smooth liberation of nitrogen was observed. In every case a high yield of the corresponding 2-substituted indazole was obtained. The



results of the thermal decompositions of 2-azidobenzylideneamines together with several azines are summarized in Table II.

The decompositions of 2-azidobenzylideneaniline (I) and 4-nitro(2-azidobenzylidene)aniline (II) yielded 2-phenylindazole[9] and 2-(4-nitrophenyl)indazole, respectively. In the case of the pyrolysis of 2,4-dinitro(2-azidobenzylidene)aniline (III) the presence of the indazole nucleus in the product, 2-(2,4-dinitrophenylamino)indazole, was substantiated by reductive cleavage to indazole.

Upon heating a solution of 2,2′-diazidobenzylideneazine (V) in either di- or trichlorobenzene, the decomposition occurred in two discrete stages. One mole of nitrogen was released at a temperature of 120–130° to yield 2-(2-azidobenzylideneamino)indazole (VI). At a temperature of 150–155°, a second mole of nitrogen was evolved and 2,2′-biindazole (VII) was produced in high yield. Both stages of the decomposition can be effected by heating V to 150° in an inert solvent producing VII in 93% yield.

A similar cyclization reaction to form the indazole nucleus was also carried out with 2-azido-2′-nitrobenzylideneazine (IV). The decomposition of IV at 150° in dichlorobenzene occurred smoothly producing a 97% yield of 2-(2-nitrobenzylideneamino)-indazole (VIII). The structural similarity of VIII and the azidoindazole (VI) mentioned earlier was established by catalytic reduction of these compounds to 2-(2-aminobenzylideneamino)indazole (IX). Further confirmation of structure IX was obtained by the conversion of the two reduction products to the identical acetamide. The possibility that a skeletal rearrange-

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