

3. It has been found that liquid ammonia will aminate haloacyl hydantoic acids which are cleaved by ordinary amination processes.

4. By the similarity of their titration curves with those of ordinary peptides it is inferred that isoelectric carbamic acid peptides are dipolar ions.

5. Cleavages of these peptides with hydrolytic agents have been studied.

6. A new source of ammonia and of carbon dioxide from the hydrolysis of proteins is suggested.

7. It is demonstrated that the isolation of a given quantity of ammonia or carbon dioxide cannot be ascribed to the presence of an equivalent amount of a certain linkage since these may be produced in non-stoichiometric proportions.

BALTIMORE, MARYLAND

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[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO., U. S. A., INC., EXPERIMENTAL RESEARCH LABORATORIES]

Catalytic Debenzylation. The Effect of Substitution on the Strength of the O-Benzyl and N-Benzyl Linkages¹

BY RICHARD BALTZLY AND JOHANNES S. BUCK

The growing synthetic importance of debenzylation procedures² in which the protective benzyl group is removed catalytically from ethers, esters and amines makes it desirable to see whether the lability of the benzyl group can be increased by convenient substitution. This would be especially useful in amine syntheses in which the N-debenzylation sometimes call for rather vigorous treatment.

Furthermore, the effect of constitutive factors on the stability of the benzyl linkages must be fundamentally related to the general scheme by which substituents on the benzene ring influence the activity of the system at various locations in the ring itself, and such influences must ultimately be accounted for in a general explanation of the behavior of aromatic systems.

The results presented here seem to give a definite answer to the practical part of the problem only. Most substitutions studied increase the stability of the benzyl linkage and the few instances in which the stability is decreased correspond to intermediates through which preparation of benzyl tertiary amines is considerably less convenient than with the unsubstituted benzyl compounds. Use of such hyperactive benzyl derivatives (involving especially the α -menaphthyl group) would be advisable only in special cases.

All the reductions here reported were performed with palladized charcoal.³ In our experience, catalyst prepared from the same batch of charcoal with constant proportions of metal used has a highly reproducible activity, as measured by the rate of reduction of benzyl alcohol. However, rates of reduction of different substances are probably only roughly comparable particularly if possible effects of hindrance be considered. This rough comparison of rates (involving in some cases a zero rate) is the only measure available to determine stability of O-benzyl linkages. It had been intended to study the competitive reduction of dibenzyl ethers until it was discovered that the substituted benzyl alcohol produced by the cleavage of the first O-benzyl bond was reduced more rapidly than the original ether, so that it was useless to seek an answer in that way.

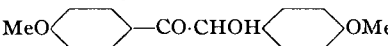
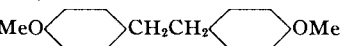
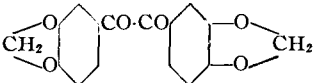
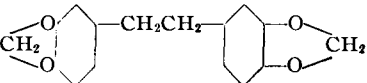
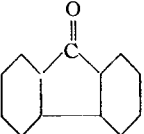
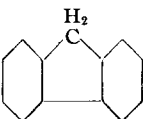
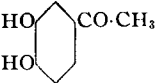
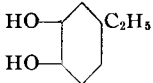
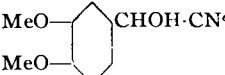
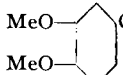
The equivalent method of competitive cleavage of dibenzylamines and dibenzylmethyamines has no such disadvantage and was used to determine the effect of substitution in the ring. It is a reasonable assumption that substitution in the ring would affect the stability of O-benzyl and N-benzyl linkages in the same fashion and a few equivalent cases in the two series (compare no. 19, Table I, with nos. 1-6, Table II) are in agree-

(1) Presented at the Detroit meeting of the American Chemical Society, April, 1943.

(2) Cf. among others Bergmann and Zervas, *Ber.*, **65**, 1192 (1932); British Patent 318,488; Baltzly and Buck, *THIS JOURNAL*, **62**, 164 (1940); Buck and Baltzly, *ibid.*, **63**, 1964 (1941); King and Work, *J. Chem. Soc.*, 1307 (1940). For a fundamentally related method see Papa, Schwenk and Whitman, *J. Org. Chem.*, **7**, 587 (1942).

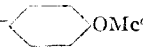

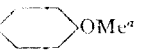


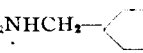
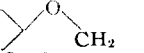
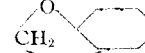
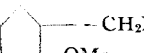
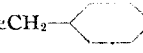
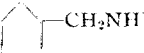
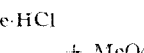

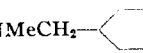
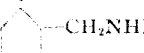
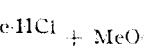
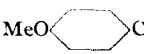
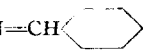
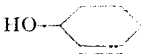
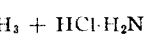

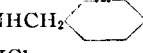
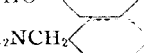
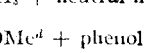




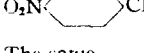
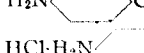
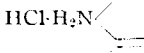
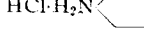
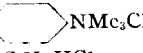
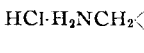

(3) Ott and Schröter, *Ber.*, **60**, 633 (1927); Hartung, *THIS JOURNAL*, **60**, 3370 (1928); Hartung and Crossley, *ibid.*, **56**, 158 (1934). These last authors consider palladium to have a greater debenzylating action than platinum in an absolute sense. Their experiments were with both metals supported on charcoal. Judged by the reduction of benzyl alcohol, palladized charcoal debenzylates more rapidly than platinum-oxide platinum-black. Use of the latter would have interfered greatly with the present experiments, in some cases preventing the debenzylation by reducing the ring and in all competitive debenzylations greatly complicating the identification of products.

TABLE I
 HYDROGENOLYSES RELATED TO O-DEBENZYLATIONS

| No. | Substance reduced | Hydrogen absorbed, mmoles. | | Product | Solvent | Rate (approx.) |
|-----|---|----------------------------|------------------------------|---|--------------|--------------------------------------|
| | | Sample, mmoles. | Calcd. ^a Observed | | | |
| 1 | $C_6H_5CH_2OH$ | 50 | 50 | $C_6H_5CH_3$ | EtOH | Very fast |
| 2 | <i>p</i> -MeOC ₆ H ₄ CH ₂ OH | 50 | 50 | <i>p</i> -MeOC ₆ H ₄ CH ₃ | EtOH | Very fast |
| 3 | <i>p</i> -MeOC ₆ H ₄ CH ₂ OCH ₂ C ₆ H ₅ | 48 | 96 | <i>p</i> -MeOC ₆ H ₄ CH ₃ + CH ₃ C ₆ H ₅ | EtOH | Very fast |
| 4 | <i>p</i> -MeOC ₆ H ₄ COCH ₃ | 50 | 100 | <i>p</i> -MeOC ₆ H ₄ C ₂ H ₅ ^b | EtOH | Fast at start with break at midpoint |
| 5 | $C_6H_5COCHMe_2$ | 100 | 200 | $C_6H_5CHOH \cdot CHMe_2$ + $C_6H_5CH_2CHMe_2$ | EtOH | Fast at start |
| 6 | $C_6H_5COCHMe_3$ | 30 | 60 | $C_6H_5CHOHCHMe_3$ | EtOH | Fast |
| 7 | $C_6H_5CH \cdot CH \cdot CH_2OH$ | 200 | 400 | $C_6H_5CH_2CH_2CH_2OH$ + $C_6H_5C_3H_7$ | EtOH | Fast |
| 8 | $C_6H_5CO \cdot CH_2C_6H_5$ | 20 | 40 | $C_6H_5CH_2CH_2C_6H_5$ | MeOH | Fast at start with break midway |
| 9 |  | 20 | 60 |  | EtOH | Moderate |
| 10 |  | 10 | 40 |  | EtOH + EtOAc | Fast, slowing at midpoint |
| 11 | $C_6H_5COC_6H_5$ ^d | 50 | 100 | $C_6H_5CH_2C_6H_5$ | MeOH | Moderate |
| 12 | $C_6H_5CHOHC_6H_5$ | 20 | 20 | $C_6H_5CH_2C_6H_5$ | EtOH | Moderate |
| 13 | $\alpha\text{-}C_{10}H_7COC_6H_5$ | 30 | 60 | $\alpha\text{-}C_{10}H_7CH_2C_6H_5$ | EtOH | Moderate |
| 14 |  | 20 | 40 |  | EtOH | Moderate |
| 15 | <i>p</i> -C ₆ H ₅ C ₆ H ₄ COC ₆ H ₅ | 40 | 80 | <i>p</i> -C ₆ H ₅ C ₆ H ₄ CH ₂ C ₆ H ₅ | EtOH + EtOAc | Slow ^e |
| 16 | $(C_6H_5)_2CH \cdot COC_6H_5$ | 10 | 20 | $(C_6H_5)_2CH \cdot CH_2C_6H_5$ | EtOH | Moderate |
| 17 | $C_6H_5CHOH \cdot CH_2OH$ | 50 | 50 | $C_6H_5CH_2CH_2OH$ (+ $C_6H_5C_2H_5$?) | MeOH | Moderate |
| 18 | $C_6H_5CO \cdot CHOH \cdot CH_3$ | 38 | 76 | $C_6H_5CHOH \cdot CHOH \cdot CH_3$ | EtOH | Moderate |
| 19 |  | 65 | 130 |  | EtOH | Slow |
| 20 |  | 20 | 60 |  | EtOH + HCl | Moderate |

^a Calculated hydrogen absorption is that required to remove the benzyl oxygen + any other expected reduction (as of a carbonyl). ^b Cf. Hartung. THIS JOURNAL. 56, 158 (1934). ^c Cf. Buck. *ibid.* 55, 2593 (1933). ^d Sample may have contained solvent. ^e Heating used to complete reduction after course was apparent.

TABLE II
 HYDROGENOLYSES RELATED TO N-DEBENZYLATIONS

| Reduction number | Substance reduced | Sample, mmoles. | H ₂ absorption, mmoles. | | Products isolated | Temp., °C. | Solvent |
|------------------|--|-----------------|------------------------------------|----------|---|------------|-------------------|
| | | | Calcd. | Observed | | | |
| 1 | $C_6H_5CH_2NMeCH_2$ -  OMe ^a HCl | 9 | 9 | 12 | MeO-  CH ₂ NHMe·HCl ^b | 25 | EtOH |
| 2 | $C_6H_5CH_2NHCH_2$ -  OMe ^d HCl | 20 | 20 | 20 | MeO-  CH ₂ NH ₂ ·HCl ^e | 65 | EtOH |
| 3 | MeO-  -CH ₂ NHCH ₂ -  -  CH ₂ HCl | 10 | 10 | 12 |  -CH ₂ NH ₂ ·HCl ^d | 75 | EtOH |
| 4 |  -CH ₂ NMeCH ₂ -  OMe HCl | 10 | 10 | ? |  -CH ₂ NHMe·HCl + MeO-  CH ₂ NHMe·HCl | 65 | EtOH |
| 5 |  -CH ₂ NMeCH ₂ -  OMe HCl | 10 | 10 | 13 |  -CH ₂ NHMe·HCl + MeO-  CH ₂ NHMe·HCl | 65 | EtOH |
| 6 | MeO-  CH ₂ N=CH-  OCH ₂ C ₆ H ₅ | 20 | 60 | 69 | HO-  CH ₂ + HCl·H ₂ NCH ₂ -  OMe ^e | 75 | EtOH + HCl |
| 7 | MeO-  CH ₂ NHCH ₂ -  OH HCl | 10 | 10 | 13 | HO-  CH ₂ + neutral mat. H ₂ NCH ₂ -  OMe ^d + phenolic base HCl | 75 | EtOH |
| 8 | Me-  -CH ₂ NMeCH ₂ C ₆ H ₅ ·HCl | 10 | 10 | 12 | Me-  -CH ₂ NHMe·HCl ^f | 25 | MeOH |
| 9 | Cl-  -CH ₂ NMeCH ₂ C ₆ H ₅ ·HCl | 10 | 10 | 12 | Cl-  -CH ₂ NHMe·HCl ^f | 25 | MeOH |
| 10 | O ₂ N-  -CH ₂ NMeCH ₂ C ₆ H ₅ ·HCl ^g | 5 | 20 | 22 | H ₂ N-  -CH ₂ NHMe·HCl ^g | 25 | EtOH |
| 11 | The same | 10 | 40 | 36 | HCl·H ₂ N-  -CH ₂ NMeCH ₂ C ₆ H ₅ ·HCl | 25 | EtOH ^h |
| 12 | The same | 10 | 40 | 45 | HCl·H ₂ N-  -CH ₂ NHMe·HCl | 65 | EtOH ⁱ |
| 13 | $C_6H_5CH_2NH$ -CH ₂ -  NMe ₃ Cl CH ₂ NMeCH ₂ C ₆ H ₅ ·HCl | 5 | 5 | 6 | HCl·H ₂ NCH ₂ -  NMe ₃ Cl | 75 | EtOH |
| 14 |  | 10 | 10 | 10 | C ₆ H ₅ CH ₂ NHMe·HCl | 25 | MeOH |

| | | | | | | | |
|---|----|----|----|----|--|----|------|
|  | 15 | 15 | 15 | 17 | The same | 25 | MeOH |
|  | 16 | 10 | 10 | 10 | C ₁₀ H ₇ CH ₂ NHMe·HCl Both amines | 25 | MeOH |
|  | 17 | 2 | 2 | 2 | C ₆ H ₅ —  —CH ₂ NHMe·HCl + C ₁₀ H ₇ CH ₂ NHMe·HCl? | 25 | MeOH |

^a V. Braun, May and Michaelis, *Ann.*, 490, 189 (1931) (only the tertiary base described; m. p. of the hydrochloride, 136–137°). ^b Tiffeneau, *Bull. soc. chim.*, [4] 9, 826 (1911), gives 168° for m. p. We found 174°. ^c Identified as the acetyl derivative, Goldschmidt and Polonowska, *Ber.*, 20, 2409 (1887). ^d Mannich and Kuphal, *Ber.*, 45, 318 (1912). ^e V. Braun, *Ann.*, 449, 249 (1926). ^f V. Braun, Michaelis and Späting, *Ber.*, 70, 1241 (1937). ^g Isolated as the dihydrochloride. ^h 130 millimoles of HCl present. ⁱ 340 millimoles of HCl present; 29 millimoles of hydrogen taken at 25°, the rest at 65°.

ment with expectation. As, however, the dibenzylamines necessary to study α -substitution were not readily available the relatively crude method of comparing rates was employed for this purpose.

Effects of α -Substitution.—Hartung and Crossley³ have already reduced a considerable number of propiophenones with palladized charcoal. Making the assumption that these reductions have the carbinol as an intermediate it can be deduced from their work that an ethyl group has relatively little effect on the rate and extent of reduction. As in our hands *p*-methoxyacetophenone absorbed the second mole of hydrogen much more slowly than the first the assumption seems justified.⁴ As, furthermore, this reduction (no. 4, Table I) is much slower than that of anisyl alcohol (no. 2) it is indicated that any alkyl group stabilizes the system somewhat. Further branching (nos. 5 and 6) continues to increase the stability: phenyl-*t*-butylcarbinol (no. 6) being unreduced at 25°. This phenomenon might be regarded as due to hindrance, but if that were the cause one would expect the reduction of the ketone to be prevented also, which is not the case.

Introduction in the α -position of another phenyl group might be expected to increase the lability of the O—C bond. On the other hand, hindrance effects make the rate in such cases unpredictable. Examples 8, 11, 12, 14 and 16 show that debenylation occurs consistently with two phenyl groups but the rates are probably not comparable. Benzoin and α -diketones are reduced consistently at a moderate rate. This last type was studied by Buck and Ide⁵ using platinum. They observed reduction of the aromatic rings accompanied by debenylation (loss of oxygen) and stripping of nuclear substituents, their products being mixtures of dicyclohexylethane and di-

(4) In regard to the statement of Hartung and Crossley, ref. 3 that no carbinol could be detected in incomplete reductions of propiophenone. Dr. Hartung writes as follows: "In a more careful study of the reduction of ketones with palladium catalyst we have been able to demonstrate to our own satisfaction that the carbinol probably is always formed as an intermediate. This is contrary to our published observations. It is true that if an active catalyst is employed there is no break in the rate of hydrogenation until two molecules of hydrogen have been taken up: however, if the reduction is interrupted it is possible to demonstrate the presence of carbinol. With an inactive catalyst, *e. g.*, one prepared in the presence of ammonium chloride, it has been possible to isolate the carbinol in yields of 85%; the carbinol was further hydrogenated with an active catalyst, to remove the hydroxyl at a rate comparable to that observed with the ketone itself."

Whether a break will or will not occur at the midpoint of the reduction curve of a ketone depends on constitutive factors which do not influence the two stages of the reduction in the same fashion.

(5) Buck and Ide. *THIS JOURNAL*, 53, 3510 (1931); 54, 820 (1932).

cyclohexylethylene glycol. At the time they were unable to interpret these results but it now seems clear that aromatic reduction and debenzilation proceeded at comparable rates. Where the aryl ring was reduced first debenzilation was, of course, prevented.⁶ Two of the four compounds that they found to resist debenzilation were re-investigated. Both these substances, anisoin and piperil (Examples 9 and 10), behaved normally with palladized charcoal, forming the corresponding diphenylethanes.

An hydroxy alkyl group in the α -position—*e. g.*, phenyl glycol (no. 17)—appears to have little more effect than a methyl in stabilizing the O benzyl linkage, but the next higher member of this series, phenylmethyl glycol (no. 18) is not reduced. A carboxyl or carbamido substitution completely prevents debenzilation as shown by failure of mandelic acid, and mandelamide to be reduced. The hydroxyl in benzoic acid is also resistant. On the other hand, a cyano substitution has no such effect. This was shown by Buck,⁷ who reduced mandelonitriles with platinum to phenethylamines. As the phenethylamines are well known to be stable under such conditions, it is apparent that debenzilation must precede hydrogenation of the CN in order to give this result. The two reactions were probably, in fact, concurrent, which accounts for the relatively poor yields obtained in certain of those reductions. We have satisfied ourselves that comparable results are obtained with palladium (Example 20).

It is difficult to determine the effect of amino methyl substitution *per se* since presence of a base inhibits debenzilation even of benzyl alcohol. This was shown by repeated failures to reduce ephedrine base, the catalyst being unable to reduce even the control substance until acid was added. In view of the fact that some hydrolysis or alcoholysis of the amine-salt must take place, however, it seems likely that ephedrine hydrochloride would be reduced if debenzilation of the base were at all facile.

(6) Cf. Levene and Stevens. *J. Biol. Chem.*, **89**, 471 (1931). These authors had a similar experience with a platinum catalyst. Cf. also Linstead, Whetstone and Levine, *THIS JOURNAL*, **64**, 2014 (1942), who mention a comparable result with *as*-octahydro-9-phenanthrol.

(7) Buck, *ibid.*, **55**, 2593 (1933). Kindler and Kwok, *Ann.*, **554**, 9 (1943), report that at 100° ethyl mandelate can be reduced to ethyl phenyl acetate and then to ethyl cyclohexyl acetate. Substitution in the ring was found to disturb this order as Kindler and Kwok believed by making the ring more reducible. We should explain it rather in that the benzyl-oxygen bond was stabilized.

An interesting parallel to the lability of the oxygen is furnished by the reduction of cinnamyl alcohol (no. 7). Here the hydrogen absorption indicated that the ethylenic bond and the hydroxyl were reduced *at about the same rate*. The product consisted of a mixture of hydrocinnamyl alcohol and propylbenzene.

Effects of Nuclear Substitution.—Owing to the superior method used, the results of this part of the work are much more precise. Contrary to our expectations all substituents in the system tended to stabilize the N-benzyl linkage. Benzyl was removed from benzyanisylmethylamine and benzyanisylamine hydrochlorides, to all appearances exclusively. Similarly the anisyl group was more labile than the piperonyl (no. 3, Table II). Methyl, chlorine and amino groups in the *para* position also stabilized the portion of the molecule to which they adhered. Through most of this work we avoided *ortho* substituents lest hindrance intervene to confuse the results. However, when 4,3'- and 4,2'-dimethoxydibenzylmethylamine hydrochlorides were reduced, it was possible in each case to isolate two secondary amine hydrochlorides, which were identified by mixed melting points. Apparently the position of substitution makes little difference. As shown by examples 6 and 7, Table II, *p*-hydroxybenzyl and *p*-methoxybenzyl are probably comparably stable, the former being somewhat more readily removed.

It was desirable to investigate the effect of some *meta*-directing groups. In general the necessary compounds were difficult to prepare, and the effect of the nitro group cannot be studied at all. An indication was furnished by the reduction of benzyl, *p*-nitrobenzylmethylamine hydrochloride. Here the benzyl group was removed readily and exclusively at room temperature. When the reduction was performed in the presence of a large excess of acid, so that the amino group produced was compelled to remain in the cationic form, the whole molecule was stabilized and cleavage ensued only upon heating, when also the benzyl came off (nos. 10, 11, 12). A similar result was obtained with a dibenzylamine having a quaternary salt grouping in one *para* position (no. 13): the substituted benzyl was stabilized and the unsubstituted exclusively removed.

The only groupings so far examined that have proved more labile than the unsubstituted benzyl

group are in effect more extended aromatic systems. Both α and β menaphthyl are removed in preference to benzyl. When these two groups were opposed to each other a mixture of secondary amines was obtained (no. 16, Table II) whose separation appeared most unpromising. The obviously impure material was, however, analytically pure showing that only methylmenaphthylamines were present and these must, therefore, have been there in comparable amounts. A probably similar situation arose in the reduction of methyl-4-phenylbenzyl- α -menaphthylamine hydrochloride except that here methyl-4-phenylbenzylamine hydrochloride, which is quite insoluble, could be isolated. It was not the sole product, however, and we believe that in this case also the two groups were comparably labile.

The only previous study of this type is that of Hartung and Crossley³ with substituted propiophenones. Their results are expressed as rates of reduction and do not permit much generalization. The work presented here is reasonably consistent within itself but we are not able to interpret it in terms of any of the current theories on the aromatic state. It is obvious that further work is required to complete the picture—especially indicated being competitive reductions involving the various groupings (Me, Cl, OMe, NH₂) that stabilize the benzyl group and similar investigation of α -substituted dibenzylamines. We are not at present in a position to continue the work, however, and wish now to present the results so far obtained.

Experimental

Reductions.—All reductions were performed with a standard preparation made (after Hartung's specifications)³ from 6 g. of charcoal (Darco G-60) and 0.6 g. of palladium (as PdCl₂). This catalyst reduces a 5-cc. sample of benzyl alcohol at a reproducible maximum—19 millimoles per minute—which is generally encountered in the second minute of reduction. Smaller samples of benzyl alcohol are reduced rapidly but with a lower maximum; they may, however, be used for control tests, where the point is merely to assure that the catalyst is unpoisoned. Such tests were always made where reduction was absent. The hydrogen absorptions observed (Tables I and II) are corrected for the hydrogen adsorbed on the catalyst (taken as 5 millimoles) which is almost instantaneous and is indicated by a sharp fall in the hydrogen pressure when shaking is begun.

The apparatus used is the modification of the Adams-Burgess-Parr machine described by Buck and Jenkins.⁸ When the volume of reduction mixture is 50 cc. a drop in

pressure of 1 lb. corresponds to absorption of 1 millimole. The reductions were carried out with 1 $\frac{1}{2}$ –3 atm. overpressure of hydrogen. Reduction was considered to be stopped when thirty minutes or more was required for a pressure-drop of 1 lb. The apparatus is usually tighter than that, but such a rate is in the order of magnitude of possible indefinite leaks. In cases where heating was required, readings were made after the apparatus had returned to room temperature and reduction was regarded as stopped when pressure was constant during heating. The error in the readings is likely to be greater when heating is used.

A reduction was considered to have failed only if the catalyst behaved normally on the addition of benzyl alcohol to the reduction mixture.

Mandelic acid and mandelamide were not reduced under these conditions. Benzilic acid and its ethyl ester showed only small and doubtful absorptions of hydrogen, and the reduction mixtures gave back the starting materials apparently unchanged.

The tertiary dibenzyl amines were usually reduced as their hydrochlorides at room temperature. The secondary dibenzyl amines regularly required heating. Solvents were ethanol or methanol, between which there is no significant difference for this purpose except when heating is required, in which case ethanol is preferable because of its lower vapor pressure. The O-debenzylations were performed at room temperature except in the case of phenyl biphenyl ketone where heating was used to save time after absorption at room temperature had already indicated that the oxygen was being removed.

Materials.—The compounds used in the O-debenzylations are all in the older literature. The solids were recrystallized to constant melting points; the liquids were purified as carefully as possible, and in no case contained catalyst poisons.

A number of the tertiary amines used are new. They were all prepared by conventional methods which are indicated in Table IV, in which are given characteristics and analytical data. The elegant Clarke methylation is not available for dibenzyl amines as cleavage ensues.

The new secondary amines that were used in the N-debenzylations are characterized in Table III. Also included here are amines produced by the debenzylation where these are new, an acetylated secondary amine (no. 11) which was an intermediate in the preparation of compound 6, and the Schiff base, no. 10.

Isolation of Products.—Most of the known products from the O-debenzylations were identified by melting point and mixed-melting points with known specimens or by analysis. *p*-Methylanisole was identified as its nitro derivative. Propylbenzene (from the reduction of cinnamic alcohol) was not obtained pure, but as a low-boiling fraction whose C–H content was far above that of any oxygen-containing derivative conceivably present. Phenylmethyl glycol, from the reduction of benzoylmethylcarbinol was an oil, presumably a mixture of stereoisomers, but analytically pure.

The solutions containing products from the N-debenzylations were evaporated *in vacuo* (after filtration from the catalyst). After reduction of benzyl, methyl, *p*-nitrobenzylamine hydrochloride, aqueous hydrochloric acid

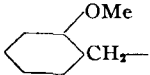

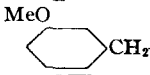
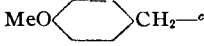

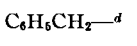

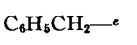

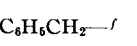
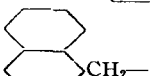
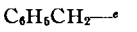
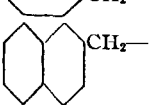

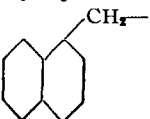
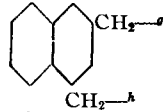
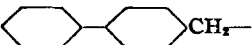

(8) Buck and Jenkins, *THIS JOURNAL*, 51, 2163 (1929).

TABLE III
 AMINE HYDROCHLORIDES, R₁R₂NH·HCl

| No. | R ₁ | R ₂ | Crystallizing solvent ^a | Appearance ^b | Empirical formula | M. p., °C. | Analyses, % | | | |
|-----|---|--|------------------------------------|-------------------------|--|------------|-------------|-----------|-------|-------|
| | | | | | | | C | Calcd. | H | Found |
| 1 | | Me ^e | AE | Colorless prisms | C ₉ H ₁₄ ONCl | 123 -123.5 | 57.57 | 7.52 | 57.76 | 7.82 |
| 2 | | Me ^e | AE | Colorless needles | C ₉ H ₁₄ ONCl | 128.5-129 | 57.57 | 7.52 | 57.62 | 7.83 |
| 3 | HCl·H ₂ N | | A | Colorless needles | C ₈ H ₁₄ N ₂ Cl ₂ | 201.5-202 | 45.93 | 6.75 | 45.94 | 6.77 |
| 4 | | | A aq. | Platelets | C ₁₆ H ₁₈ O ₃ NCl | 246- 247 | 62.42 | 5.90 | 62.49 | 6.29 |
| 5 | | HO | AE | | C ₁₀ H ₁₆ O ₂ NCl | 179 -179.5 | 64.39 | 6.49 | 64.46 | 6.60 |
| 6 | ClMe ₂ N | C ₆ H ₅ CH ₂ - ^d | AE | Hygroscopic solid | C ₁₇ H ₂₄ N ₂ Cl ₂ | 164 (dec.) | 62.37 | 7.40 | 62.09 | 7.57 |
| 7 | | Me ^h | AE | | C ₁₂ H ₁₄ NCl | 189.5-190 | 69.37 | 6.80 | 69.00 | 6.95 |
| 8 | | Me ^e | A | Colorless plates | C ₁₄ H ₁₆ NCl | 265 (dec.) | 71.92 | 6.90 | 71.81 | 7.17 |
| 9 | ClMe ₂ N | | A | Oblique prisms | C ₁₀ H ₁₆ N ₂ Cl ₂ | 223 -223.5 | N. 11.82 | Cl. 29.91 | 11.87 | 29.86 |
| 10 | C ₆ H ₅ CH ₂ O | | Hexane | | C ₂₂ H ₂₁ O ₂ N | 82 | 79.90 | 6.39 | 79.83 | 6.66 |
| 11 | C ₆ H ₅ CH ₂ N | | AE | | C ₁₉ H ₂₅ ON ₂ Cl | 130 -130.5 | 68.53 | 7.57 | 68.45 | 7.72 |

^a A = abs. ethanol; E = abs. ether; A aq. = aqueous ethanol. ^b Appearance is noted only where crystals were well-formed and of distinctive shape. ^c By reduction of Schiff base. ^d By reduction of Schiff base of anisaldehyde and piperonylamine. ^e By reduction of Schiff base (substance 10). ^f From debenzoylation. ^g From hydrolysis of substance 11. ^h From α -menaphthyl chloride and methylamine. ⁱ By the sequence: $p\text{Me}_2\text{NC}_6\text{H}_4\text{CHO} + \text{C}_6\text{H}_5\text{CH}_2\text{NH}_2 \longrightarrow \text{Schiff base} \longrightarrow \text{Me}_2\text{NC}_6\text{H}_4\text{CH}_2\text{NHCH}_2\text{C}_6\text{H}_5 \longrightarrow \text{acetyl derivative} \longrightarrow \text{methiodide} \longrightarrow \text{methochloride}$.

TABLE IV
 TERTIARY DIBENZYLAMINE HYDROCHLORIDES. $R_1R_2NMe \cdot HCl$

| No. | R_1 | R_2 | Crystallizing solvent ^a | Appearance ^b | Empirical formula | M. p., °C. | Analyses, % | | | |
|-----|---|---|------------------------------------|-------------------------|-----------------------|-------------|-------------|--------|-------|-------|
| | | | | | | | C | Calcd. | H | Found |
| 12 |  |  | AE | Prisms | $C_{17}H_{22}O_2NCl$ | 160 -161 | 66.32 | 7.21 | 66.61 | 7.52 |
| 13 |  |  | AE | Prisms | $C_{17}H_{22}O_2NCl$ | 159 -160.5 | 66.32 | 7.21 | 66.22 | 7.25 |
| 14 |  |  | AE | Needles | $C_{16}H_{20}NCl$ | 161 -162 | 73.40 | 7.71 | 73.59 | 7.83 |
| 15 |  |  | AE | Needles | $C_{15}H_{17}NCl_2$ | 145.5-146.5 | 63.83 | 6.09 | 63.58 | 6.19 |
| 16 |  |  | A | Pale yellow prisms | $C_{15}H_{20}N_2Cl_2$ | 182.5-183 | 60.19 | 6.74 | 60.18 | 7.00 |
| 17 |  |  | AE | Needles | $C_{19}H_{24}NCl$ | 225 | 76.60 | 6.77 | 76.57 | 6.95 |
| 18 |  |  | AE | Prisms | $C_{19}H_{20}NCl$ | 194 -195 | 76.60 | 6.77 | 76.42 | 6.67 |
| 19 |  |  | AE | Platelets | $C_{23}H_{22}NCl$ | 230.5-231 | 79.40 | 6.38 | 79.66 | 6.52 |
| 20 |  |  | AÆ | | $C_{25}H_{24}NCl$ | 211.5-212 | 80.28 | 6.47 | 80.36 | 6.72 |

^a A = abs. ethanol; E = abs. ether; Æ = ethyl acetate. ^b Appearance noted only where crystal form is distinctive. ^c From anisyl chloride and secondary amines (compounds 1 and 2). ^d From benzyl chloride and methyl-*p*-methylbenzylamine. ^e From benzylmethylamine with appropriate halide. ^f By reduction of nitro compound. ^g From β -menaphthyl bromide and compound 7. ^h From α -menaphthyl chloride and compound 8.

was added before evaporation to take care of the newly formed amino group. The residual hydrochlorides were crystallized from polar-non-polar solvent mixtures, usually alcohol-ether. Except with reductions 4-7 and 16-17 (see Table II) the material as first obtained was substantially homogeneous; the melting point did not change significantly on further crystallization and the quantity obtained was approximately that to be expected.

With the reductions 4 and 5 the first product obtained was fairly pure methyl-*p*-anisylamine hydrochloride. The material in the mother liquors was, however, much lower melting and slow crystallization showed different crystal forms to be present. Fractional crystallization of mechanically separated portions resulted in the isolation of methyl-*o*-methoxybenzylamine hydrochloride and of methyl-*m*-methoxybenzylamine hydrochloride which were compared with synthetic specimens.

After the reductions 6 and 7 (which are substantially equivalent), evaporation was carried out at atmospheric pressure. A considerable fraction of *p*-cresol was separated and also a small neutral fraction. The hydrochlorides permitted separation into anisylamine hydrochloride and a small amount of phenolic base. The amount of the latter did not suffice for identification, and the difficulty in its isolation from the mixture was such as to permit no accurate estimation of the quantity originally present.

The reduction 16 furnished about the expected amount of hydrochloride which was obviously impure, but which analyzed correctly for $C_{12}H_{14}NCl$. Separation of a pure substance appeared hopeless so we can only say that both methyl menaphthylamines were present.

Reduction 17 also gave a non-homogeneous mixture of

hydrochlorides from which methyl-4-phenylbenzylamine hydrochloride was separated readily. We believe methyl α -menaphthylamine to have been present but could not demonstrate it with the material available.

The authors are indebted to Mr. W. S. Ide for the many micro-analyses recorded here, and also for a number performed upon previously known substances (to confirm identification) and not included in the tables.

Summary

1. The effect of substituents on the stability of O-benzyl and N-benzyl bonds has been investigated through catalytic hydrogenolysis (debenzylation).

2. Alkyl groups in the α -position of benzyl alcohol stabilize the system somewhat, carboxyl and amino groups much more so. Aryl and cyano groups may labilize the system but at any rate do not stabilize it.

3. Substitution on the aromatic rings with $-OMe$, $-OH$, $-NH_2$, $-Cl$, $-NR_3Cl$ and $-CH_3$ gives greater stability.

4. More extended aromatic systems as in menaphthyl and 4-phenylbenzyl are more labile than benzyl.

TUCKAHOE, N. Y.

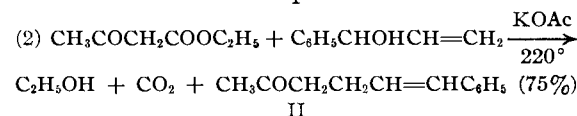
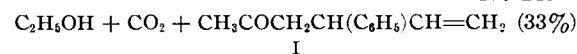
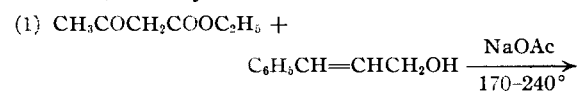
RECEIVED MAY 29, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Rearrangement of Allyl-Type Esters of β -Keto Acids

By WALTER KIMEL AND ARTHUR C. COPE

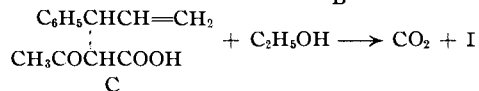
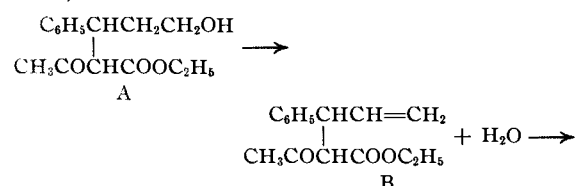
Carroll reported recently that β, γ -unsaturated alcohols react with ethyl acetoacetate in the presence of alkaline catalysts to give unsaturated ketones.¹ The course of the reaction may be illustrated with cinnamyl alcohol and phenylvinylcarbinol, which yielded isomeric ketones.



An addition mechanism was suggested for the reaction, bearing a formal resemblance to the

(1) Carroll, (a) *J. Chem. Soc.*, 704 (1940); (b) 1266 (1940); (c) 507 (1941).

Michael condensation. According to this interpretation, the intermediates in reaction (1) would be A, B and C.



While this interpretation would account for the attachment of the $\text{CH}_3\text{COCH}_2^-$ group to the γ -carbon atom of the alcohol employed, objections may be raised to it. The mechanism requires that the hydroxymethyl group, $-\text{CH}_2\text{OH}$, shall activate the ethylenic double bond suffi-