supra), which have been established to be independent of the formation of carbonium ions, "hot" or "cold." The operation of several competing modes of reaction would seem to render unnecessary the postulate of a special "hot" carbonium ion.

Experimental

trans-Cyclohexanol-2-*d*.—In a typical experiment, 46.8 g. of cyclohexene oxide was reduced with 5.0 g. of lithium aluminum deuteride in ether. The product was distilled through a small column to yield 24.5 g. (51% yield), b.p. 156.5–159.5°, $n^{23.1}$D 1.4649–1.4656, $d^{25.4}_4$ 0.9539. Freshly distilled cyclohexanol had $n^{23.1}$D 1.4653, $d^{25.3}_4$ 0.9448. The density of the deuterioalcohol corresponds to 0.96 deuterium atom per molecule.[30]

trans-Cyclohexyl-2-*d* *p*-Toluenesulfonate.—In a typical experiment 10.1 g. of *trans*-cyclohexanol-2-*d* was added to 20.9 g. of *p*-toluenesulfonyl chloride in 40 cc. of dried pyridine in an ice-bath and was stirred at 0° for 5 hours. After pouring into 1 l. of ice-cold water and extracting with petroleum ether, the organic phase was washed and dried. Cooling in a Dry Ice-bath gave 19.6 g. of product, m.p. 44.0–44.6°. A second crop of 2.0 g. also was obtained giving a combined yield of 85%.

cis-Cyclohexyl-2-*d* Acetate.—A solution of 21.6 g. of *trans*-cyclohexyl-2-*d* *p*-toluenesulfonate and 19.6 g. of potassium acetate in 100 cc. of absolute alcohol was refluxed for 21 hours. The mixture was poured into ice-water containing sodium carbonate and was extracted with ether. The dried ether extract was distilled yielding 0.99 g. (8.2%) of acetate, b.p. 100–108° (76 mm.), $n^{20.5}$D 1.4390–1.4400.

cis-Cyclohexanol-2-*d*.—The *cis*-cyclohexanol-2-*d* acetate above was treated with 0.6 g. of lithium aluminum hydride in 40 cc. of ether. The product was distilled, collecting 0.46 g. of alcohol, b.p. 147–8°, $n^{22.6}$D 1.4556.

cis-Cyclohexylamine-2-*d*.—A mixture of 52.8 g. (0.207 mole) of *trans*-cyclohexyl-2-*d* tosylate and 20.8 g. of sodium azide in 400 ml. of acetone and 100 ml. of water was refluxed for 22 hours. More water was added and the acetone was distilled; the residual oil was steam distilled and the distillate was saturated with salt and extracted with ether. The dried ether solution was added to 6.8 g. (0.18 mole) of lithium aluminum hydride in ether. After the addition of water, the ether solution was dried and distilled. The yield, after a second distillation, was 1.8 g. (9%) of amine, $n^{21.0}$D 1.4571, b.p. 131–134°.

Deamination of *cis*-Cyclohexylamine-2-*d*.—To a solution of 1.57 g. (0.0157 mole) of *cis*-cyclohexylamine-2-*d* in 10 ml. of water cooled in an ice-bath, was added 3.14 ml. of 6 *N* perchloric acid, and then 1.30 g. of sodium nitrite in 6 ml. of water. After stirring in an ice-bath for 7 hours, 0.25 ml. of 6 *N* perchloric acid and 0.2 g. of sodium nitrite were added. After 22 hours in an ice-bath and 8 hours at room temperature, the mixture was saturated with salt and extracted with ether. The dried ether extract was distilled yielding 0.27 g. of product, b.p. 155–157° (17%). The infrared spectrum contained a band at 6.1 μ indicative of nitrate ester. This band as well as a few others including a sharp band at 6.4 μ indicative of impurities was not present in an alcohol sample purified by vapor phase chromatography with a silicone oil on Celite column. Samples of the *cis*- and *trans*-alcohols were purified in the same manner for comparison purposes. We are indebted to Miss Mary R. S. Weir for these purifications. The infrared spectra used for the quantitative analysis were taken on thin films of the pure liquids in a 0.035-mm. microcell using a Baird Atomic infrared spectrophotometer with sodium chloride optics run at "slow" speed.

BERKELEY, CALIF.

(30) A. MacLean and R. Adams, THIS JOURNAL, **58**, 804 (1936).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Reduction of Aromatic Acids and Amides by Sodium in Liquid Ammonia

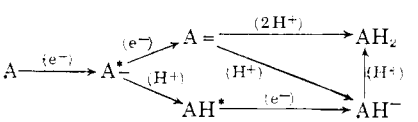
BY M. E. KUEHNE AND B. F. LAMBERT

RECEIVED NOVEMBER 24, 1958

A number of aromatic acids and amides were reduced with sodium in liquid ammonia. Variations in the type of product obtained in these reactions are explained in terms of differing mechanistic pathways. The formation of either dihydro or tetrahydro products is a function of the acidity and positional bond stability of an initial diene. Thus benzoic acid and N-acetyl-*p*-aminobenzoic acid led to 1,4-dihydrobenzoic acid; *p*-toluic acid to 1,2,3,4-tetrahydro-*p*-toluic acid and 1,4-dihydro-*p*-toluic acid; *m*-methoxybenzoic acid to 1,2,3,4-tetrahydro-5-methoxybenzoic acid; 3,4,5-trimethoxybenzoic acid to 1,4-dihydro-3,5-dimethoxybenzoic acid. With ethanol, the amide function is reduced in benzamide, but with *t*-butyl alcohol 1,4-dihydrobenzamide is obtained. Using ethanol, *m*-methoxybenzamide is reduced only with a very large excess of sodium to the 1,4-dihydro product. 3,4,5-Trimethoxybenzamide and a number of N-monosubstituted derivatives led to the corresponding 1,4-dihydro-3,5-dimethoxybenzamides.

The reduction of aromatic compounds by liquid ammonia solutions of alkali metals and a proton source such as alcohol,[1] has experienced a rapid development, led primarily by the school of Birch.[2,3] However reports of simple 2,5-cyclohexadiene carboxylic acids and their derivatives have been limited to 1,4-dihydro-*o*-toluic acid,[4] the unstable 1,4-dihydro-*o*-anisic acid[5] and a 1,4-dihydro-3-methoxybenzoic acid which constitutes ring E of a modified yohimban skeleton.[6] 1,4-Dihydrobenzoic acid[7] was described at the time of writing of this publication.

While it is most probable that the over-all mechanism of these reductions involves addition of two electrons to an aromatic system, followed by protonation of the organic anions,[2,3,8] a more detailed mechanism has remained the subject of much speculation. A number of variants were proposed.[2,3] Thus the reduction of an aromatic molecule A could proceed through protonation of a dianion, either simultaneously or successively or by protonation of an initial ion radical, followed by further reduction and protonation.



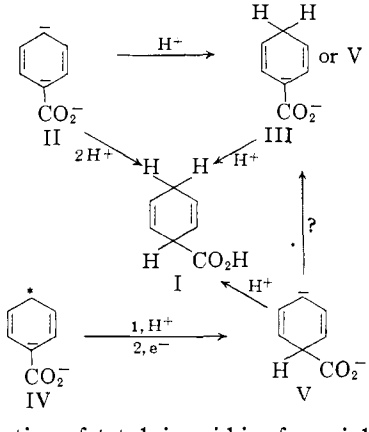
(1) G. W. Watt, *Chem. Revs.*, **46**, 317 (1950).
(2) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950).
(3) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958).
(4) A. J. Birch, *J. Chem. Soc.*, 1551 (1950).
(5) M. E. McEntee and A. R. Pinder, *ibid.*, 4419 (1957).
(6) F. L. Weisenborn and H. E. Applegate, THIS JOURNAL, **78**, 2021 (1956).
(7) H. Plieninger and G. Ege, *Angew. Chem.*, **70**, 505 (1958).
(8) New evidence in favor of the nascent hydrogen theory was presented by W. Hückel, M. Maier, E. Jordan and W. Seeger, *Ann.*, **614**, 47 (1958).

It was hoped that some insight into this problem would be gained from an examination of the reduction products obtained from aromatic compounds carrying substituents which have a stabilizing or destabilizing effect on negative charges and radicals without being subject to reductive alteration. While carboxyl and amide groups stabilize a negative charge or radical, alkyl substituents stabilize only the latter and even lower the stability of a carbanion.

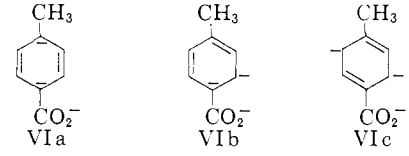
In the following examination of individual cases, it will be seen that benzoic acid, *o*-toluic acid[4] and 3,4,5-trimethoxybenzoic acid yield the normal 1,4-dihydro products but that *p*-toluic acid and *m*-anisic acid give mainly tetrahydrobenzoic acids. An analysis within the mechanistic framework indicated above will attempt to show why such a difference can be expected, and that these results can be interpreted by either pathway.

Reduction of benzoic acid with sodium in liquid ammonia gives a high yield of the diene acid I. Analytical results of all fractions obtained on distillation of the reaction product were in agreement with 1,4-dihydrobenzoic acid, showing that little, if any, tetrahydro compound could have been formed. The position of the double bonds is rigidly established by a lack of ultraviolet absorption which would be expected for structures in which the double bonds are conjugated with each other or the carboxyl group.

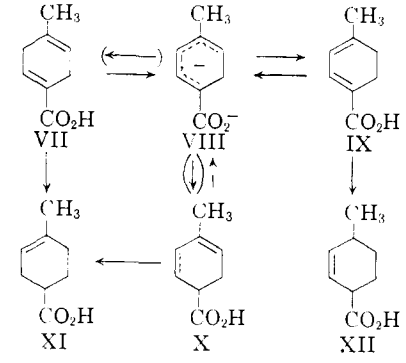
This product conforms readily to any of the three mechanistic possibilities mentioned above. The position of the double bonds is determined by irreversible protonation of carbanions at the site of maximum charge density. In the anion II, maximum concentration of anionic character is located by the mutual repulsion of the two charges and stabilization of one charge by the carboxylate substituent. In the anion III, derived from stepwise protonation of II and even in an anion V, the maximum charge density is still found in the center of the substituted 1,4-pentadiene system rather than at the end of a conjugated substituted 1,3-pentadiene.[4,9]



The reduction of *p*-toluic acid is of special interest insofar as one could expect two stereoisomeric 1,4-dihydro products and a knowledge of the ratio of *cis*- to *trans*-1,4-dihydro-*p*-toluic acid might enable a further refinement of the mechanistic picture. In *p*-toluic acid a complication is, however, introduced by differentiating a second ring position from the others in its ability to function as site of a radical or anionic charge. Unlike the reduction of benzoic acid, the reduction of *p*-toluic acid leads by the first mechanism to a dianion in which there is a choice of having maximum charge density at a tertiary or a secondary carbon. Since a secondary carbanion is favored over a tertiary carbanion, one can expect an increase of charge density *meta* to the methyl-substituted carbon and a decrease of charge density at that tertiary position. Thus the optimum location of maximum charge density may not be represented only by VIa but contributions such as VIb and especially VIc become significant.



By simultaneous protonation of a dianion, the reduction of *p*-toluic acid should thus give, at least in part, an α,β-unsaturated acid VII (from VIc) as initial product. The diene acid VII possesses two hydrogens which are not only allylic to two double bonds but are vinylogously adjacent to a carboxyl group. The acidity of these hydrogens is thus considerable, favoring an equilibrium of VII with the mesomeric anion VIII in the basic reaction medium. The same anion VIII is also the result of the first addition in stepwise protonation of the dianion VIc. By either mechanism the initial reduction product of *p*-toluic acid should thus be derived from protonation of the mesomeric anion VIII.



While irreversible protonation takes place at the site of maximum charge density, it is found that the point of proton attachment in the product of a reversible process is determined by the resultant structure with the greatest stability. Protonation of the mesomeric anion VIII therefore leads to the fully conjugated diene acid IX.

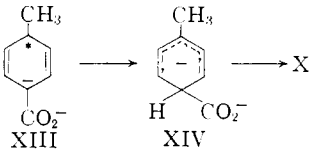
Since the fully conjugated isomer IX, as well as the less probable alternate initial products VII and X, are subject to further reduction, one may expect *p*-toluic acid to be reduced to tetrahydro products such as XI and especially XII.

(9) The importance of the geometric center of charge as determinant of the point of protonation, in addition to the atom with the maximum charge density, has been pointed out by G. S. Hammond, THIS JOURNAL, **77**, 334 (1955), and this concept has been used implicitly in the following discussion.

The unconjugated diene products normally obtained from sodium-liquid ammonia reductions can be equilibrated to the more stable conjugated dienes by treatment with stronger base.[2] In the reduction of *p*-alkylated aromatic acids one encounters a mesomeric anion corresponding to a conjugate acid stronger than those usually found in the reduction of benzenoid compounds. In contrast to those other reductions, reversible protonation of the anion is possible and a fully conjugated diene carboxylic acid can be formed as initial product.

Comparison of the contributing resonance structures of the mesomeric anion VIII from *p*-toluic acid with those of the anions III or V, utilized in the reduction of benzoic acid, suggests a lower stability of the latter and thus supports the experimental observation that with III or V protonation by an irreversible process is given preference.

If the reduction of *p*-toluic acid proceeds by protonation of a radical anion XIII, followed by electron addition, the mesomeric anion XIV is formed. Maximum charge density would again not be expected at the tertiary position and thus protonation *ortho* to the carboxyl group leads to the diene X, which is, however, also a conjugate acid of the mesomeric anion VIII and therefore part of the pattern outlined above.



XIII XIV

In any of these mechanisms, protonation at a tertiary position *para* to the carboxyl group and subsequent isomerization of a 1,4-dihydro product is unlikely since the second process would not be expected to be subject to the sharp distinction found experimentally between benzoic acid, *o*-toluic acid and *p*-toluic acid.

The foregoing considerations are reflected in the experimental findings. From the reduction of *p*-toluic acid a mixture of acids is obtained which can be divided into liquid and solid products. On catalytic reduction of the total mixture, 0.92 equivalent of hydrogen was absorbed, as calculated for a tetrahydro-*p*-toluic acid. Disproportionation, which has been observed with 1,4-dihydrobenzenes on hydrogenation catalysts,[10] could account for a low uptake of hydrogen by the reaction product even if much 1,4-dihydro-*p*-toluic acid were present. This possibility was ruled out, however, by showing that no increase in ultraviolet absorption occurred after prolonged stirring of the material under nitrogen with the same catalyst and solvent.

Careful fractionation of the liquid produced only 1,2,3,4-tetrahydro-*p*-toluic acid (XII), of which neither the *cis* nor the *trans* isomer has been described in the literature. On catalytic hydrogenation, an analytically pure sample of the fractionated liquid consumed one equivalent of hydrogen and led to an apparent mixture of the known *cis*- and *trans*-hexahydrotoluic acids. Although the *trans* isomer, m.p. 112°,[11] could be identified, it is assumed that the liquid acid product is the corresponding *cis* isomer, m.p. 13°.[12]

The residue from fractionation consisted mainly of *p*-toluic acid formed by autoxidation. While oxidation would be expected primarily for a dihydro toluic acid, it was found that the 1,2,3,4-tetrahydro-*p*-toluic acid fractions obtained above were slowly oxidized to *p*-toluic acid on standing in the open.[13]

Repeated recrystallization of the solid reduction products yielded a material without ultraviolet absorption, which analyzed correctly for the expected 1,4-dihydro-*p*-toluic acids. The melting point range, which could not be constricted by fractional crystallization, suggests a mixture of *cis* and *trans* epimers. Due to the facile autoxidation to *p*-toluic acid, the bulk of initial crystalline material could not be fully characterized by fractional crystallization and it is thus not impossible that 1,2,3,6-tetrahydro-*p*-toluic acid, m.p. 99°,[14] is formed in small amounts in the reduction of *p*-toluic acid. Utilization of vapor phase chromatography for a more precise analysis of the reaction mixture was not successful.

In alternate attempts to determine the ratio of *cis*- to *trans*-1,4-dihydro products from the reduction of *p*-substituted benzoic acids, we turned to two cases in which the orientation of the substituent might have a greater effect on the properties of the products.

Unfortunately the reduction products of terephthalic acid were found to have ill defined, high decomposition points which made them unsuitable for quantitative characterization.

The reduction of *p*-aminobenzoic acid was carried out in the usual way, but isolation of a pure dihydro compound was not possible from the mixture of salts obtained. Purification was complicated by rapid autoxidation to the aromatic starting material.

By following a reduction of *m*-anisic acid with direct hydrolysis of the reduction mixture, Birch[15] obtained a high yield of 3-carboxycyclohexanone, rather than the anticipated α,β-unsaturated keto acid. Carrying out this reduction in a similar fashion, we were able to isolate the intermediate enol ether acid. Although distillation of this material was accompanied by decarboxylation, fractions were obtained which analyzed well for a tetrahydroanisic acid.

In this instance, the formation of a monoölefin, which under presently considered conditions necessitates an intermediate with a conjugated double bond, can only be explained by assigning the hydrogen alpha to the carboxyl group in 1,4-dihydro-3-methoxybenzoate, corresponding to the anion XVI, an acidity greater than that of the corresponding hydrogen in 1,4-dihydrobenzoate. An electrically analogous stabilization of anionic substituents placed *ortho* to a methoxyl group on aromatic rings, XV, has been observed[2] and can be ascribed to an

(10) F. Richter and W. Wolff, *Ber.*, **63**, 1721 (1930).

(11) W. H. Perkin and S. S. Pickles, *J. Chem. Soc.*, 639 (1905).

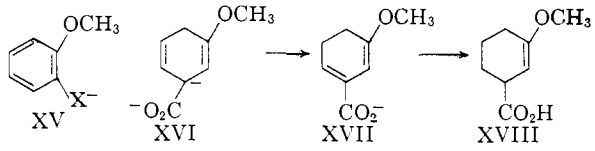
(12) G. H. Keats, *ibid.*, 2003 (1937).

(13) Similarly the formation of benzoic acid from the 1,2,3,4-tetrahydro compound has been noted by E. J. Boorman and R. P. Linstead, *ibid.*, 261 (1935).

(14) E. Lehmann and W. Paasche, *Ber.*, **68**, 1069 (1935).

(15) A. J. Birch, P. Hextall and S. Sternhell, *Australian J. Chem.*, **7**, 256 (1954).

inductive effect. Stabilization by a hydrogen bridge[2] from the methoxyl group to the anion is precluded in XVI by the steric arrangement of a *trans* substituted double bond.



XV XVI XVII XVIII

Thus reversible protonation of anion XVI becomes possible, leading to a conjugated system XVII which is in turn subject to further reduction to the tetrahydroanisic acid XVIII.

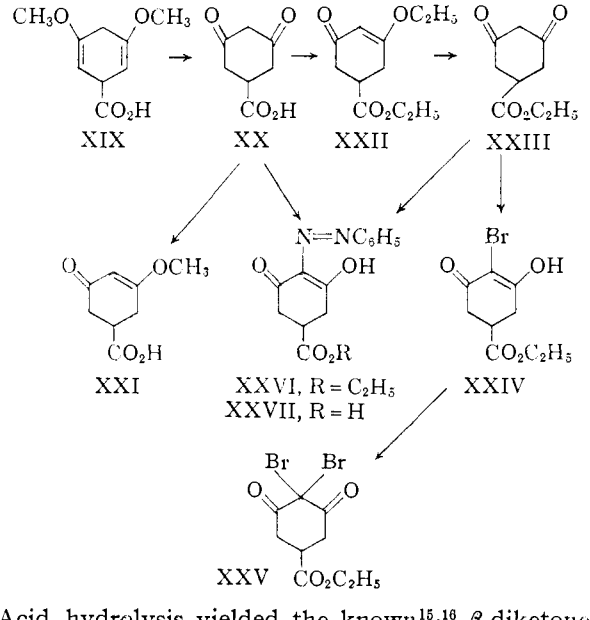
From the reduction of 3,4,5-trimethoxybenzoic acid the 1,4-dihydro product XIX, lacking the *p*-methoxyl group, is obtained in high yield. Formation of this compound could be inferred by Birch[15] from the 3,5-diketocyclohexanecarboxylic acid (XX) obtained on acid treatment of the reaction mixture.

Conjugation of the double bonds and subsequent overreduction is prevented here due to stabilization of the double bonds by the attached methoxyl groups. However the equilibrium of double bond isomers can be displaced to the less favored conjugated structure by irreversible removal of this product. Thus treatment of the reaction mixture with strong base leads to *m*-anisic acid.[15]

In the reduction of aromatic acids, *p*-substituents other than methoxyl groups can be eliminated, provided that they will form stable anions. Thus we have found that the reduction of *p*-acetamidobenzoic acid yields acetamide and 1,4-dihydrobenzoic acid.

Chart A illustrates a few products derived from 1,4-dihydro-3,5-dimethoxybenzoic acid (XIX).

CHART A



XIX XX XXII XXIII XXI XXVI, R = C_2H_5 XXVII, R = H XXIV XXV

Acid hydrolysis yielded the known[15,16] β-diketone XX which was converted to the acid enol ether XXI on solution in methanol and to the ester enol ether XXII by azeotropic removal of water from a benzene–ethanol solution. Mild acid hydrolysis of XXII gave the diketo ester XXIII, characterized as the monobromide XXIV and dibromide XXV as well as by the product XXVI of coupling with phenyldiazonium chloride. Similarly the diketo acid XX could be converted to a phenylazo compound XXVII.

The sodium–liquid ammonia reduction of amides derived from secondary amines and aromatic acids has been found to be a useful method for the preparation of the corresponding aromatic aldehydes.[17] However, the reduction of aromatic amides formed from ammonia or primary amines has not been described, though it has been said that in the presence of ethanol, reduction of the amide function to a benzylic alcohol and subsequent reductive cleavage to the methyl compound would preceed reduction of the aromatic ring.[18] Indeed, we found in several attempts to reduce benzamide with 3.3 equivalents of sodium in the presence of ethanol, that no isolatable quantities of dihydro- or tetrahydrobenzamides were produced. Reduction had taken place at the carbonyl group. Since in these compounds one should be able to protect the functional group from reduction by formation of an anion, analogous to the process utilized in aromatic acids, it was expected that 1,4-dihydrobenzamides could be formed under appropriate conditions.

The aromatic amides differ from the acids in that they lead to anions of higher energy or, in other words, that they are less acidic. The introduction of substituents into the aromatic ring which would help to stabilize the amide anion could make the amide sufficiently acidic to render it immune to reduction. Thus while the amide group is reduced in benzamide, *m*-methoxybenzamide is recovered unchanged when subjected to 3.3 equivalents of sodium in ammonia and ethanol. The degree of stabilization by the methoxyl substituent, which causes such a great difference in the course of reaction, is seen from a comparison of the acidities of benzoic acid (pK 4.20) and *m*-methoxybenzoic acid (pK 4.09). When a large excess of sodium is used in the reduction of *m*-methoxybenzamide, analogous to conditions for the reduction of anisole,[19] the expected 1,4-dihydro-3-methoxybenzamide is obtained.

It was found that in the reduction of *m*-methoxybenzoic acid a large excess of sodium was not necessary. The energy increase in going from the aromatic system to an initial ion-radical must thus be smaller when the anionic charge is stabilized by a carboxylate ion than when it is stabilized by an amide ion. While *m*-methoxybenzoic acid is readily reduced by an equivalent amount of sodium, an excess must be used in the case of the amide to satisfy the reaction with ethanol, competing here at a comparable rate.

The reduction of benzamide to 1,4-dihydrobenzamide was achieved in high yield by using *t*-butyl alcohol in place of ethanol. By using a less acidic

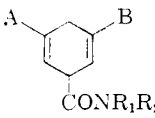
(16) E. E. van Tamelen and G. T. Hildahl, THIS JOURNAL, **78**, 4405 (1956).

(17) A. J. Birch, J. Cymerman-Craig and M. Slaytor, *Australian J. Chem.*, **8**, 512 (1955).

(18) A. J. Birch, *J. Roy. Inst. Chem.*, **81**, 100 (1957).

(19) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

TABLE I



A	B	R_1	R_2	Emp. formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	M.p., °C.	Solvent	Yield, %
OCH_3	H	H	H	$C_8H_{11}NO_2$	62.73	62.51	7.24	7.13	9.15	9.39	158–160	Benzene–petr. ether	30
OCH_3	OCH_3	H	H	$C_9H_{13}NO_3$	59.00	59.33	7.15	7.22	7.64	7.69	155–156	Benzene–chloroform	90(73)
OCH_3	OCH_3	H	CH_3	$C_{10}H_{15}NO_3$	60.90	61.08	7.67	7.68	7.10	6.84	120–121	Cyclohexane–methylene chloride	56(49)
OCH_3	OCH_3	H	C_2H_5	$C_{11}H_{17}NO_3$	62.54	62.68	8.11	8.24	6.63	6.50	113–114	Benzene	90(64)
OCH_3	OCH_3	H	$CH(CH_3)_2$	$C_{12}H_{19}NO_3$	63.97	64.11	8.50	8.48	6.22	6.04	140–141	Benzene	74(55)
OCH_3	OCH_3	H	$C(CH_3)_3$	$C_{13}H_{21}NO_3$	65.24	65.26	8.85	9.14	5.85	5.97	93–94	Benzene–petr. ether	8(2)
OCH_3	OCH_3	H	CH_2CH_2OH	$C_{11}H_{17}NO_4$	58.13	58.16	7.54	7.53	6.17	6.04	114–115	Benzene–methylene chloride	33
OCH_3	OCH_3	H	CH_2COOH	$C_{11}H_{15}NO_5$	54.76	54.40	6.27	6.21	5.81	6.13	140–141	Methanol	40
OCH_3	OCH_3	H	CH_2CONH_2	$C_{11}H_{16}N_2O_4$	54.99	55.02	6.71	6.94	11.66	11.74	151–155	Methanol–benzene	10
OCH_3	OCH_3	CH_3	CH_3	$C_{11}H_{17}NO_3$	62.52	62.59	8.10	8.27	6.63	6.43	102–103	Benzene–cyclohexane	6
OC_2H_5	OC_2H_5	H	H	$C_{11}H_{17}NO_3$	62.52	62.37	8.10	8.34	6.63	6.90	153–155	Ethanol	82

proton source, stabilization of the amide as its anion became possible and the competing rate of reaction of sodium with the proton source was cut down to a negligible extent. Quantitative reduction was found with 3.3 equivalents of the alkali metal. 1,4-Dihydrobenzamide is a stable crystalline compound which was observed to disproportionate completely when a solution in ethanol was stirred with 10% palladium-on-charcoal catalyst for five hours at room temperature.

3,5-Dimethoxybenzamide, 3,4,5-trimethoxybenzamide and a number of its N-alkylated derivatives were reduced to the corresponding 1,4-dihydro-3,5-dimethoxybenzamides. The results have been summarized in Table I. Yields are generally more indicative of the properties of the products than of differences in the reductions. When considerable losses were observed on recrystallization, yields are given for the crude and pure product. One case deserves special attention: Table I shows the yield of the 1,4-dihydrobenzamide obtained from reduction of N-*t*-butyl-3,4,5-trimethoxybenzamide to be very much smaller (2%) than that from reduction of other monosubstituted trimethoxybenzamides and to be comparable to the yield of dihydroamide obtained on reduction of N,N-dimethyl-3,4,5-trimethoxybenzamide (6%). Thus, with the nitrogen as part of a neopentyl-type system, the amide behaves as one which cannot be stabilized by a negative charge. An inspection of molecular models does not reveal prohibitive steric hindrance to any of the resonance forms of the anion. The experimental results therefore suggest that a bulky, solvated sodium cation or direct solvation of the anion may play an important role in stabilization of the amide.

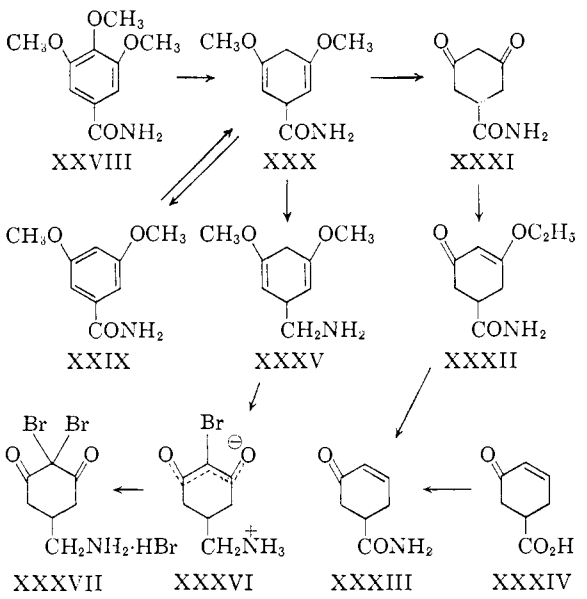
A direct comparison of the extent of amide reduction was obtained from small scale experiments using benzamide, *m*-methoxybenzamide and 3,5-dimethoxybenzamide. Ultraviolet spectra of the total reaction mixtures obtained with 10% excess of sodium showed only 3% of reduction for *m*-methoxybenzamide, compared with about 70% for the other compounds. Absorption of moisture and the use of a larger amount of ethanol may explain the presence of aromatic material on a small scale where it was not found preparatively, but cannot account for an almost total recovery found again for *m*-methoxybenzamide.

From the reduction of 3,4,5-trimethoxybenzimide, 1,4-dihydro-3,4-dimethoxybenzamide was obtained as the only crystalline product. Here the observed cleavage is, however, not related to the reduction since it was found in a control experiment that 3,4,5-trimethoxybenzimide is almost entirely cleaved by stirring for ten minutes in liquid ammonia containing an amount of ethanol and sodium ethoxide corresponding to that formed in the actual reduction.

A few conversions of the reduction product XXX of 3,4,5-trimethoxybenzamide and 3,5-dimethoxybenzamide are depicted in chart B. Apart from rigidly establishing the identity of the dihydrobenzamides, these reactions demonstrate their versatility as synthetic intermediates.

Hydrolysis of 1,4-dihydro-3,5-dimethoxybenzamide (XXX) with dilute aqueous acid gave the β-diketone XXXI, which on digestion with ethanol

CHART B



formed a monoenol ether XXXII. Reduction of this ketone with sodium borohydride, followed by acid hydrolysis, yielded the ene-one amide XXXIII. This product was identical with a sample prepared from 3-keto-4-cyclohexenecarboxylic acid (XXXIV)[20] using the mixed anhydride method for formation of the amide.

Lithium aluminum hydride reduction of 1,4-dihydro-3,5-dimethoxybenzamide (XXX) and distillation of the product gave a clear oil consisting of a mixture of about equal amounts of 3,5-dimethoxybenzylamine and the corresponding 1,4-dihydro compound XXXV. The aromatic component presumably arises from autoxidation of XXXV during work-up. It will be shown that this process is catalyzed by base and can thus be expected to attain special prominence in the handling of dihydro products with amine substituents.

While the dihydro compound XXXV could not be purified readily and recrystallization of a 2,4-dinitrophenyl derivative prepared from the mixture led only to the pure derivative of 3,5-dimethoxybenzylamine, acid hydrolysis to the β-diketone and formation of a crystalline monobromide XXXVI and dibromide XXXVII, were adequate for characterization. It is of interest that the monobromo derivative XXXVI exists as a zwitterion. Thus there is no carbonyl absorption above 1610 cm.$^{-1}$. The medium sized peak at this wave length is followed by stronger bands at 1590 and 1560 cm.$^{-1}$ which may be compared with the absorption of an amino acid carboxylate anion (1600–1560 cm.$^{-1}$) of which the zwitterion XXXVI is a vinylog.

If 3,4,5-trimethoxybenzamide is reduced and worked up in the usual fashion except that the addition of ammonium chloride is omitted, it is found that 3,5-dimethoxybenzamide is obtained in high yield as the only crystalline product. Similarly, the base catalysis of autoxidation of the diene amides can be demonstrated by their conversion to the corresponding aromatic compounds when stirred in a basic solution open to the air. In the absence of base these compounds are considerably more stable and can be stored as crystalline solids without appreciable change in melting point.

Pharmacological screening of the compounds described in this publication revealed a mild sedative activity for a number of the alkoxy benzamides listed in Table II and an increase of this activity in some of the corresponding reduction products. Subsequent to these findings favorable clinical results have been reported for the use of N-3,4,5-trimethoxybenzoylglycine diethylamide as a weak sedative.[21]

Acknowledgment.—Microanalyses and the recording of infrared and ultraviolet spectra were carried out by our Analytical Research Division. We thank Mr. L. Dorfman and his staff for their prompt and excellent service and their friendly cooperation. Mr. C. C. Chu assisted ably in the laboratory during the initial experiments.

Experimental

1,4-Dihydrobenzoic Acid (I).—A solution of 10.0 g. (0.082 mole) of benzoic acid in 100 ml. of ethanol and 600 ml. of liquid ammonia was stirred and 6.2 g. (0.27 mole) of sodium added in small pieces, followed by 14.6 g. (0.27 mole) of ammonium chloride. The ammonia was evaporated and the residual material dissolved in 500 ml. of ice-water. After acidification with 10% hydrochloric acid, the solution was extracted with four 100-ml. portions of ether, the ether washed once with saturated sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo*. The remaining pale yellow oil was distilled at 96–98° (0.01 mm.) giving 9.0 g. (89% yield) in four fractions, showing no ultraviolet absorption above 220 mμ.

Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.49. Found: Fraction 1: C, 67.64; H, 6.47; $n^{20}D$ 1.6112; Fraction 2: C, 67.58; H, 6.51; $n^{20}D$ 1.6111; Fraction 3: C, 67.83; H, 6.30; $n^{20}D$ 1.6113; Fraction 4: C, 67.99; H, 6.42; $n^{20}D$ 1.6115.

Addition of 0.40 g. (0.0038 mole) of phenylhydrazine to a solution of 0.50 g. (0.0040 mole) of the acid obtained above, in 1.5 ml. of benzene and cooling in ice gave the crystalline hydrazine salt, m.p. 80–81°. A sample was recrystallized for analysis from benzene–petroleum ether without change of melting point.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.78; H, 7.00. Found: C, 67.44; H, 6.96.

Reduction of 10.0 g. (0.058 mole) of N-acetyl-*p*-aminobenzoic acid, dissolved in 50 ml. of ethanol and 400 ml. of liquid ammonia with 5.6 g. (0.24 mole) of sodium, followed by addition of 14.0 g. (0.26 mole) of ammonium chloride and working up gave 5.4 g. (75% yield) of distilled oil with the very characteristic odor of 1,4-dihydrobenzoic acid. A phenylhydrazine salt, formed by the above procedure, showed no depression in a mixed melting point with the sample obtained from the reduction product of benzoic acid. In addition to 1,4-dihydrobenzoic acid, 1.7 g. of acetamide was obtained, identical with an authentic specimen in mixed melting point and infrared spectrum as well as by analysis.

Reduction of *p*-Toluic Acid.—A stirred solution of 40.0 g. (0.29 mole) of *p*-toluic acid in 300 ml. of ethanol and 1800 ml. of liquid ammonia was reduced with 22.8 g. (0.99 mole) of sodium, added slowly in small portions. At completion of the reaction, 60.0 g. (1.1 moles) of ammonium chloride was added and the ammonia allowed to evaporate. After addition of 300 ml. of ice-water and acidification with 10% hydrochloric acid, the reaction mixture was extracted with 1000 ml. of methylene chloride in five portions. The extracts were washed three times with water and saturated salt

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TABLE II

N-MONOSUBSTITUTED 3,4,5-TRIMETHOXYBENZAMIDES EXAMINED FOR SEDATIVE ACTIVITY AND USED IN PART FOR REDUCTION

Substituent	Emp. formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	M.p., °C.	Solvent
CH_3	$C_{11}H_{15}NO_4$	58.67	58.56	6.71	6.68	6.22	6.14	138–139	Benzene
C_2H_5	$C_{12}H_{17}NO_4$	60.24	60.46	7.16	7.23	5.85	5.59	115–116	Benzene
$CH(CH_3)_2$	$C_{13}H_{19}NO_4$	61.64	61.81	7.56	7.48	5.53	5.22	153–154	Methylene chloride–benzene
$C(CH_3)_3$	$C_{14}H_{21}NO_4$	62.90	63.14	7.92	7.91	5.24	5.05	139–140	Benzene
CH_2CH_2OH	$C_{12}H_{17}NO_5$	56.46	56.14	6.71	6.77	5.49	5.43	123–124	Methylene chloride–benzene
CH_2COOH	$C_{12}H_{15}NO_6$	53.54	53.41	5.62	5.76	5.21	5.24	221–222	Ethanol
CH_2CONH_2	$C_{12}H_{16}N_2O_5$	53.72	53.70	6.01	5.73	10.43	10.54	171–172	Methanol (forms methanolate)
$CH_2CON(CH_3)_2$	$C_{14}H_{20}N_2O_5$	56.73	56.54	6.80	6.70	9.45	9.14	122–123	Benzene
$CH_2CON(C_2H_5)_2$	$C_{16}H_{24}N_2O_5$	59.24	59.14	7.46	7.44	8.63	8.32	133–134	Water
$CH_2CON(CH_2)_4$	$C_{16}H_{22}N_2O_5$	59.61	59.71	6.88	6.91	8.69	8.82	131–132	Methanol–ether
$CH_2CON(CH_2)_2O(CH_2)_2$	$C_{16}H_{22}N_2O_6$	56.79	56.49	6.55	6.54	8.28	8.06	168–169	Ethanol
$CH_2CH_2N(C_2H_5)_2$	$C_{16}H_{26}N_2O_4$	61.91	61.56	8.44	8.31	9.03	9.44	95–96	Benzene–ether
$(CH_2)_2N(CH_2)_2O(CH_2)_2$	$C_{16}H_{24}N_2O_5$	59.24	59.39	7.46	7.41	8.64	8.68	147–148	Methylene chloride–benzene (forms hydrate)
$(CH_2)_3N(C_2H_5)_2$	$C_{17}H_{28}N_2O_4$	62.96	62.89	8.69	8.54	8.64	8.42	68–69	Ether–petr. ether
$CHCH_3(CH_2)_3N(C_2H_5)_2$	$C_{19}H_{32}N_2O_4$	64.74	64.70	9.15	9.06	7.98	8.06	103–104	Methylene chloride–benzene
$(CH_2)_2NH(C_{10}H_{11}O_4)$[a]	$C_{22}H_{28}N_2O_8$	58.92	58.84	6.30	6.24	6.25	6.06	245–246	Acetic acid
$C_{10}H_{11}O_4$[a]	$C_{20}H_{23}NO_8$	59.25	59.47	5.72	5.77	3.45	3.41	190–191	Methanol–ether

[a] $C_{10}H_{11}O_4$ = 3,4,5-trimethoxybenzoyl.

solution, dried over magnesium sulfate and concentrated *in vacuo* to give 39.5 g. of oily product.

This oil (3.9 g.) was distilled from an oil-jacketed flask at a jacket temperature of 96–118° (0.005 mm.) giving 3.6 g. of clear, colorless distillate; ultraviolet λ_{max} 233 (log ϵ 2.88) in ethanol. Attempts at vapor phase chromatography using a Perkin–Elmer Vapor Fractometer, model 154, with a number of different columns, showed no satisfactory resolution of the mixture.

Purification of the "liquid fraction": The remaining 35.6 g. of material was chilled in an ice-bath, causing complete solidification, and was then permitted to return to room temperature. Filtration of the semi-solid gave 25.1 g. of a liquid which was dissolved in a small amount of petroleum ether, chilled in ice and filtered again. After removal of the petroleum ether *in vacuo* and distillation from an oil-jacketed flask at a jacket temperature of 90–120° (0.001 mm.), 18.7 g. of oil was obtained which solidified on chilling in ice. After warming to room temperature, 3.7 g. of oily solid was again filtered off and the remaining 15.0 g. of liquid subjected to slow fractionation through a 45-cm. column packed with glass helices. Four fractions, together 8.5 g., b.p. 64–65° (0.07 mm.), were obtained with the bulk of material collected in the central fractions. All fractions solidified by chilling in ice but were liquid at 25°. The material showed no ultraviolet absorption above 220 mμ but on standing in the open for five days, a λ_{max} 235 (log ϵ 3.45), in ethanol, was found.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: Fraction 2: C, 68.63; H, 8.50; $n^{24}D$ 1.4790; Fraction 3: C, 68.54; H, 8.40; $n^{25}D$ 1.4795.

The distillation residue of 6.1 g. consisted of crude *p*-toluic acid.

Hydrogenation of 1,2,3,4-tetrahydro-*p*-toluic acids: A solution of 1.21 g. (0.0087 mole) of fraction 2, obtained above, in 50 ml. of ethanol, was subjected to hydrogenation using 100 mg. of 10% palladium-on-charcoal catalyst. The rapid uptake of hydrogen stopped at 220 ml. (about 0.0091 mole at 22°). Filtration and concentration gave 1.21 g. of an oil containing solid material. Recrystallization of the solid from water followed by recrystallization from ligroin produced a sample, m.p. 112° (reported[11] 112° for *trans*-hexahydro-*p*-toluic acid).

Purification of the "solid fraction": The oily residues from filtration of the chilled "liquid fraction" before its distillation from the jacketed flask were combined. Treatment with petroleum ether gave 3.2 g. of solid, m.p. 130–140°, softening at 40°, with λ_{max} 235 (log ϵ 3.70) in ethanol. This material contained too much *p*-toluic acid to allow isolation of other compounds by fractional crystallization. From the mother liquor the balance of material was obtained as an oil, solidifying only when kept in ice and thus constituting a further quantity of the "liquid fraction."

The residue from filtration, after distillation from the jacketed flask (3.7 g.) was similarly divided into 1.5 g. of

solid, m.p. 65–90°, and 2.2 g. of liquid. Repeated recrystallization of the solid from ligroin gave a sample, m.p. 65–80°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.76; H, 7.52.

Repetition of the reduction of *p*-toluic acid under identical conditions, but omitting the "liquid fraction" purification and concentrating on the isolation of a maximum amount of solid material, working as rapidly as possible to prevent autoxidation, yielded in the best case 20% of solid, m.p. 67–87°. On fractional crystallization from ligroin or water, samples were obtained with a m.p. 97–100°, softening at 89°, showing analyses consistent with the above and no absorption in the ultraviolet above 220 mμ.

Hydrogenation of the total reduction product: *p*-Toluic acid (40.0 g.) was reduced in liquid ammonia and the mixture of products distilled from a jacketed flask as indicated above, yielding 35.6 g. of material. A solution of this product in 50 ml. of ethanol was subjected to catalytic hydrogenation at 20°, using 2.0 g. of 10% palladium-on-charcoal catalyst. Consumption of hydrogen stopped after a rapid uptake of 5145 ml.

A solution of 4.14 g. of the sodium–ammonia reduction product, taken as aliquot from a similar preparation, was stirred for 15 hr. with 0.22 g. of 10% palladium-on-charcoal catalyst in 50 ml. of ethanol under an atmosphere of nitrogen. Nitrogen was passed through the stirred mixture of solvent and catalyst for 30 min. before the olefinic material was introduced. No ultraviolet absorption above 220 mμ could be found for this solution either before or after stirring with the catalyst.

3-Methoxy-1,4,5,6-tetrahydrobenzoic Acid (XVIII).—A solution of 20.0 g. (0.13 mole) of *m*-methoxybenzoic acid in 1200 ml. of liquid ammonia and 200 ml. of ethanol was reduced with 9.95 g. (0.43 mole) of sodium, added in small pieces to the stirred solution. On completion of the reaction, 27.0 g. (0.50 mole) of ammonium chloride was added, the ammonia slowly evaporated by standing at room temperature and the residue taken up in 400 ml. of ice-water. Gradual acidification with 10% hydrochloric acid and frequent intermittent extraction with methylene chloride was continued until the solution reached *p*H 4. The extracts were then washed with water and saturated sodium chloride solution, dried over magnesium sulfate and evaporated *in vacuo* to give 20.0 g. of crude product. Distillation from a jacketed flask at a bath temperature of 125° (0.3 mm.) was accompanied by much decomposition; 6.4 g. of a clear oil was collected which was redistilled from a conventional apparatus, b.p. 78–84° (0.02 mm.), giving 3.13 g. of oil accompanied again by much decomposition.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.78; H, 7.48.

1,4-Dihydro-3,5-dimethoxybenzoic Acid (XIX).—To a solution of 31.8 g. (0.15 mole) of 3,4,5-trimethoxybenzoic acid in 225 ml. of ethanol and 1500 ml. of liquid ammonia was added 18.0 g. (0.78 mole) of sodium in small pieces, followed by 75.0 g. (1.4 moles) of ammonium chloride. The ammonia was evaporated and the residue taken up in 2 l. of ice-water. Alternate additions of small portions of 10% hydrochloric acid and immediate extraction with methylene chloride were carried out until the solution became acidic to congo red. The combined extracts were washed several times with water, dried over magnesium sulfate, filtered and concentrated *in vacuo* at room temperature. Trituration of the residue with a small amount of ether and filtration gave 17.7 g. of product. Concentration of the ether yielded an additional 6.3 g. of white crystalline product. The crude material, m.p. 100–105° dec. (87% yield), could be recrystallized from ether–hexane. A sample prepared for analysis showed a m.p. 105° dec. or 118° dec. depending on the rate of heating.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.56. Found: C, 58.75; H, 6.58.

3,5-Diketocyclohexanecarboxylic Acid (XX).—A suspension of 80.0 g. (0.43 mole) of 1,4-dihydro-3,5-dimethoxybenzoic acid in 800 ml. of 2% hydrochloric acid was heated on the steam-bath for 15 min. The clear solution was then concentrated to dryness *in vacuo*, the residue triturated with a small amount of ether and filtered, giving 66.0 g. of the diketone (97%) as a white, crystalline compound, m.p. 182° (lit.[16] m.p. 178–180°).

3-Keto-5-methoxy-4-cyclohexene-1-carboxylic Acid (XXI).—A solution of 0.20 g. (0.0013 mole) of 3,5-diketocyclohexanecarboxylic acid in 5 ml. of absolute methanol was chilled in ice after standing for 24 hr. at room temperature. On addition of a few drops of ether, 0.15 g. of the enol ether crystallized, m.p. 192–193°. Recrystallization from methanol–ether gave a pure sample, m.p. 194–195° (yield 69%); ultraviolet absorption λ_{max} 247–249 (log ε 4.20) in methanol.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.48; H, 5.92. Found: C, 56.71; H, 5.91.

3-Hydroxy-4-phenylazo-5-keto-3-cyclohexene-1-carboxylic Acid (XXVII).—To a solution of 0.46 g. (0.02 mole) of sodium in 30 ml. of methanol was added 1.56 g. (0.01 mole) of 3,5-diketocyclohexanecarboxylic acid. The solution was cooled in a salt–ice-bath and aqueous phenyldiazonium chloride prepared from 0.93 g. of aniline (0.01 mole), added dropwise over 30 min., with stirring, keeping the reaction temperature at −4 to −8°. After standing for one additional hour at −5°, the crystalline material was filtered off, washed with water, ethanol and ether; 2.3 g. of product (89% yield) was obtained. Samples were recrystallized from ethanol or dioxane–water, m.p. 215° dec., ultraviolet λ_{max} (log ε): 222 (3.70), 244 (3.97), 248–251 (3.90), 387–393 (4.27).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.61; H, 4.72; N, 10.62.

3,5-Diketo-1-carbethoxycyclohexane (XXIII).—A suspension of 1.6 g. (0.0075 mole) of 3-ethoxy-5-carbethoxy-2-cyclohexenone (XXII) (prepared[16] from XX) in 20 ml. of water and 0.5 ml. of 10% hydrochloric acid was heated on a steam-bath. After 10 min. the clear solution was concentrated *in vacuo* to 1.35 g. of a colorless gum, insoluble in benzene or ether, sparingly soluble in methylene chloride and very soluble in water. The product could not be crystallized and was best characterized by bromination or condensation with phenyldiazonium chloride.

4-Bromo-3,5-diketo-1-carbethoxycyclohexane (XXIV).—A solution of 1.35 g. (0.0075 mole) of XXIII in 15 ml. of acetic acid was cooled in an ice-bath; 1.0 g. (0.0080 mole) of sodium acetate trihydrate was then added, followed by 1.17 g. (0.073 mole) of bromine in 10 ml. of acetic acid. The solvent was removed *in vacuo* and the residue taken up in methylene chloride. After filtering off the sodium bromide, the solution was concentrated to a gummy residue which was treated with a small amount of water and then with benzene to give 1.6 g. of crystalline product (82% yield). A sample of the material was recrystallized for analysis from methylene chloride–benzene, m.p. 129–130°, ultraviolet absorption λ_{max} 287–289 (log ε 4.17) in ethanol at 0.00531 mg. per ml. (position of maximum dependent on concentration).

Anal. Calcd. for $C_9H_{11}BrO_4$: C, 41.08; H, 4.22; Br, 30.38. Found: C, 41.34; H, 4.14; Br, 29.94.

4,4-Dibromo-3,5-diketo-1-carbethoxycyclohexane (XXV).—To a solution of 1.27 g. (0.0069 mole) of XXXIII in 13 ml. of glacial acetic acid was added 2.0 g. (0.015 mole) of sodium acetate trihydrate followed by 2.26 g. (0.14 mole) of bromine in 10 ml. of acetic acid. The solvent was removed at room temperature *in vacuo* and the residue triturated with benzene. After removal of sodium bromide and sodium acetate by filtration, addition of heptane caused 1.7 g. (72% yield) of dibromide to crystallize out; m.p. 62–65°. Repeated recrystallizations from benzene–heptane gave a pure sample, m.p. 77–78°.

Anal. Calcd. for $C_9H_{10}Br_2O_4$: C, 31.61; H, 2.94; Br, 46.73. Found: C, 32.01; H, 3.09; Br, 46.40.

3-Carbethoxy-5-hydroxy-6-phenylazo-5-cyclohexene-1-one (XXVI).—Phenyldiazonium chloride, prepared from 0.93 g. of aniline (0.01 mole), was added to a solution of 1.84 g. (0.01 mole) of XXIII and 0.80 g. (0.02 mole) of sodium hydroxide in 30 ml. of ethanol. During the dropwise addition the reaction was stirred in a salt–ice-bath at −10°; 50 ml. of water was added and the acidic reaction mixture filtered. After washing the precipitate with water and ether, 2.4 g. (83%) of crude product was obtained which could be recrystallized from ethanol, m.p. 125–126°; ultraviolet absorption λ_{max} (log ε): 223 (3.72), 245 (4.03), 251 (4.01), shld. 386 (4.33), 398–401 (4.34).

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.81; H, 5.64; N, 9.71.

Preparation of Benzamides from Table II.—All amides, except for N-(3,4,5-trimethoxybenzoyl)-glycine, which was prepared by the usual Schotten–Baumann procedure, were prepared by adding a solution of the acid chloride in benzene to a cooled solution of three equivalents of the particular amine in benzene. Filtration and washing of the precipitate with water, extraction of the washings with methylene chloride and concentration of the filtrate and extracts gave amide products which were recrystallized from the solvents indicated in Table II.

3,4,5-Trimethoxybenzimide was prepared from 3,4,5-trimethoxybenzoyl chloride and 3,4,5-trimethoxybenzamide in pyridine according to the procedure for benzimide.[22]

Preparation of Amides of N-(3,4,5-Trimethoxybenzoyl)-glycine.—A suspension of 26.9 g. (0.10 mole) of N-(3,4,5-trimethoxybenzoyl)-glycine and 22.9 g. (0.11 mole) of phosphorus pentachloride in 270 ml. of acetyl chloride was stirred for 18 hr. at room temperature, then filtered and the crude acid chloride washed twice with 25-ml. portions of acetyl chloride and twice with 200-ml. portions of petroleum ether. The crude acid chloride was added directly, with stirring, to a large excess of the liquid amine in question. After standing overnight, the reaction mixtures were concentrated to dryness *in vacuo* in the case of the higher boiling amines and the products recrystallized.

Reduction of 3,4,5-Trialkoxybenzamides. General Procedure.—A solution of 0.040 mole of amide in 120 ml. of ethanol and 680 ml. of liquid ammonia was stirred rapidly and 4.6 g. (0.20 mole) of sodium added over 5 min. When the reaction was complete, as seen by a disappearance of blue coloration, 21 g. (0.40 mole) of ammonium chloride was added and the ammonia allowed to evaporate by standing at room temperature; 500 ml. of water was then added and the reaction mixture extracted thoroughly with methylene chloride. The extracts were washed with water and sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo*. The products were recrystallized from the solvents indicated in Table I. All compounds were checked for absence of aromatic contaminants by ultraviolet spectra.

Exceptions: (a) In the reduction of N,N-dimethyl-3,4,5-trimethoxybenzamide only 3.9 g. (0.17 mole) of sodium was used with 100 ml. of ethanol, 580 ml. of liquid ammonia and 9.0 g. (0.17 mole) of ammonium chloride. The solvents were removed *in vacuo* and the dry residue leached with 1200 ml. of methylene chloride. Concentration and distillation of the residue from an oil-jacketed flask (bath temperature 140–180°) at 0.2 mm. gave 10 g. of liquid in two layers with the heavier one crystallizing on cooling to give the diene amide.

(b) For the reduction of N-(3,4,5-trimethoxybenzoyl)-glycine, 5.6 g. (0.24 mole) of sodium was used with 100 ml. of ethanol, 600 ml. of liquid ammonia and 14 g. (0.26 mole) of ammonium chloride. After evaporation of the ammonia and addition of ice-water, the solution was cautiously acidified to *p*H 3 and filtered. The bulk of product was thus obtained directly. A further quantity resulted from extraction with methylene chloride, in which the product is only sparingly soluble.

(c) The reduction of N-(3,4,5-trimethoxybenzoyl)-glycine amide was carried out with 5.6 g. (0.24 mole) of sodium. To ensure complete solubility, 200 ml. of ethanol and 1200 ml. of ammonia were used. Following the addition of 14 g. (0.26 mole) of ammonium chloride the solvents were removed *in vacuo* and the dry residue leached with two 40-ml. portions of ice-water. The residual gum was then taken up in 25 ml. of methylene chloride from which the product crystallized on chilling.

1,4-Dihydro-3-methoxybenzamide.—A solution of 3.2 g. (0.021 mole) of *m*-methoxybenzamide in 25 ml. of ethanol and 320 ml. of liquid ammonia was reduced by addition of 3.6 g. (0.16 mole) of sodium; 15.0 g. (0.28 mole) of ammonium chloride was then added, the ammonia evaporated off and the reaction mixture poured into 200 ml. of water. The solution was clarified by filtration and extracted thoroughly with methylene chloride. The extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo;* 3.1 g. of material, m.p. 105–130° was thus obtained. Recrystallization from benzene–petroleum ether gave 1.0 g. of dihydro product, m.p. 158–160°.

(22) A. W. Titherley, *J. Chem. Soc.*, **85**, 1673 (1904).

Study of the Extent of Reduction.—Solutions of 1.0 g. each (0.0083 mole, 0.0066 mole, 0.0055 mole) of benzamide, *m*-methoxybenzamide and 3,5-dimethoxybenzamide in 50 ml. of ethanol and 300 ml. of ammonia were reduced with 0.63 g. (0.027 mole), 0.50 g. (0.022 mole) and 0.42 g. (0.018 mole), respectively, of sodium. Ammonium chloride 1.70 g. (0.032 mole), 1.29 g. (0.024 mole) and 1.08 g. (0.20 mole), was added to the solution and all solvent removed *in vacuo*. The dry residues were then each dissolved in 1000 ml. of methanol and ultraviolet spectra taken of aliquot portions.

	λmax, mμ	log ε	Found log ε	Reduct., %
Benzamide	223	4.035	3.338	74
m-Methoxybenzamide	290	3.350	3.338	3
3,5-Dimethoxybenzamide	247	3.681	3.228	65
	299	3.371	2.863	69

1,4-Dihydro-3,5-dimethoxybenzamide (XXX).—(a) A sample of 3,4,5-trimethoxybenzamide (XXVIII) was reduced as indicated in the general procedure above. The product (crude yield 90%) was recrystallized to practical purity from benzene–chloroform (73% yield), m.p. 150–152°; analytical sample, m.p. 155–156°; infrared absorption: 3460, 3450 (N–H); 1690 (enol ether); 1670 (amide C=O); in chloroform.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64; OCH_3, 33.88. Found: C, 59.33; H, 7.22; N, 7.69; OCH_3, 31.27.

(b) To a solution of 3.5 g. (0.017 mole) of 3,5-dimethoxybenzamide (XXIX) in 30 ml. of absolute ethanol and 180 ml. of liquid ammonia, 1.3 g. (0.057 mole) of sodium was added, followed by 10.0 g. (0.19 mole) of ammonium chloride after completion of the reaction. The crude product, 3.0 g., obtained as above, was recrystallized to give 1.8 g. of compound, m.p. 153–156° (59% yield). A mixed melting point of the products from sequences a and b showed no depression.

3,5-Dimethoxybenzamide (XXIX).—From 3,4,5-trimethoxybenzamide (XXVIII): A solution of 5.0 g. (0.024 mole) of 3,4,5-trimethoxybenzamide (XXVIII) in 36 ml. of ethanol and 200 ml. of liquid ammonia was reduced with 2.8 g. (0.12 mole) of sodium. No ammonium chloride was added after the reaction. Following the evaporation of ammonia, the mixture was poured into water and extracted 5 times with 40-ml. portions of methylene chloride. The extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated *in vacuo* to give 3.7 g. of residue. Crystallization from chloroform–benzene resulted in 3.2 g. of the dimethoxybenzamide, m.p. 145–146° (75% yield). An analytical sample was obtained by recrystallization, m.p. 146–147°.[23]

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.95; H, 6.16; N, 7.95.

From 1,4-dihydro-3,5-dimethoxybenzamide (XXX): A suspension of 1.0 g. (0.0047 mole) of 1,4-dihydro-3,5-dimethoxybenzamide (XXX) in 15 ml. of ethanol containing 2.0 g. (0.044 mole) of sodium ethoxide was stirred for 15 hr. at room temperature in an open flask. A clear solution resulted after several hours. The reaction mixture was poured into water and extracted well with chloroform. The extracts were washed with water, dried over magnesium sulfate and evaporated to give 0.80 g. of residue. Two crystallizations from chloroform–benzene gave 0.50 g. of the dimethoxybenzamide (XXIX), m.p. 146–147° (50% yield).

For comparison 3,5-dihydroxybenzamide (Aldrich Chem. Co.) was converted to the dimethyl ether with dimethyl sulfate and sodium hydroxide in the usual way. The product, m.p. 146–147°, showed no depression on mixed melting point with either of the samples obtained above.

1,4-Dihydrobenzamide.—A stirred solution of 15.0 g. (0.124 mole) of benzamide in 200 ml. of dry *t*-butyl alcohol and 1200 ml. of liquid ammonia was reduced with 9.66 g. (0.42 mole) of sodium. After completion of the reaction, 30.0 g. (0.56 mole) of ammonium chloride was added and the ammonia allowed to evaporate. The reaction mixture was then concentrated to dryness *in vacuo* at room temperature, 350 ml. of water added and the slurry extracted 10 times with 100-ml. portions of methylene chloride. After

(23) F. Mauthner, *J. prakt. Chem.*, [2] **87**, 405 (1862).

washing twice with water, once with saturated salt solution and drying over magnesium sulfate, the extracts were concentrated *in vacuo*, triturated with petroleum ether and 12.5 g. (82% yield) of crude product collected, m.p. 141–147°. After two recrystallizations from benzene 10.5 g., m.p. 150–152°, was obtained. The initial crude product and the purified material showed only end absorption in the ultraviolet and no maximum at 224 mμ. A sample was recrystallized for analysis, m.p. 154–155°.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.24; H, 7.35; N, 11.30.

Disproportionation: (a) After passing nitrogen through a suspension of 0.10 g. of 10% palladium-on-charcoal catalyst in 100 ml. of ethanol for 1 hour, 0.50 g. of 1,4-dihydrobenzamide was added and the mixture stirred under a nitrogen atmosphere for 5 hr. After filtering, the ultraviolet absorption of an aliquot portion showed a λ_{max} 224 mμ (log ε 3.84) accounting for a 50% conversion to benzamide.

(b) A solution of 1.50 g. (0.012 mole) of 1,4-dihydrobenzamide in 30 ml. of ethanol was hydrogenated at atmospheric pressure using 0.10 g. of 10% palladium-on-charcoal catalyst. After 2 hr. at 23° the rapid uptake of hydrogen had stopped at 170 ml. (0.0076 mole). Filtration and concentration gave a mixture of products from which 0.60 g. of hexahydrobenzamide, m.p. 185–186°, was isolated by recrystallization; reported[24] m.p. 185–186°.

3,5-Diketocyclohexanecarboxamide (XXXIII).—A suspension of 10.0 g. (0.055 mole) of 1,4-dihydro-3,5-dimethoxybenzamide (XXX) in 50 ml. of 3% aqueous hydrochloride acid was heated on a steam-bath for 10 min. The clear solution was then concentrated to dryness *in vacuo*, leaving 8.5 g. of the diketone as a white, crystalline mass, m.p. 200–205° dec. (yield 100%). A sample was purified for analysis by recrystallization from water; m.p. 208–210° dec., ultraviolet absorption λ_{max} 257 mμ (log ε 4.17) in ethanol; λ_{max} 256 mμ (log ε 4.20) 0.1 *N* HCl; λ_{max} 281 mμ (log ε 4.37) 0.1 *N* KOH; infrared 3130, 3270 (N–H); 1670 (amide C=O); 1610, 1560 (β-diketone) cm.$^{-1}$, in Nujol.

Anal. Calcd. for $C_7H_9NO_3$: C, 54.17; H, 5.89; N, 9.03. Found: C, 53.91; H, 5.88; N, 8.98.

3-Ethoxy-5-keto-3-cyclohexenecarboxamide (XXXII).—Three 100-ml. portions of absolute ethanol were slowly distilled from a flask containing 17.8 g. (0.11 mole) of 3,5-diketocyclohexanecarboxamide (XXXI). The residue was recrystallized once from absolute ethanol to give 11.7 g. of the enol ether (yield 56%), m.p. 200–203°. The materials showed infrared absorption at 1590 cm.$^{-1}$ and no absorption at 1560 cm.$^{-1}$, characteristic of the diketo amide starting material. A sample was purified for analysis by recrystallization from ethanol, m.p. 205–206°, ultraviolet λ_{max} 251 mμ (log ε 4.20) in ethanol; infrared 3140, 3270 (N–H); 1670 (amide C=O); 1630, 1590 (COC=COC_2H_5) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64. Found: C, 59.07; H, 7.10; N, 7.91.

3-Keto-4-cyclohexenecarboxamide (XXXIII).—(a) To a suspension of 0.50 g. (0.0027 mole) of 3-ethoxy-5-keto-3-cyclohexenecarboxamide (XXXII) in 20 ml. of methanol, cooled in ice, 0.50 g. (0.013 mole) of sodium borohydride was added with stirring, in portions of 0.10 g. at 30-min. intervals. After standing at room temperature for 20 hr., the reaction mixture was poured into an iced solution of 4 ml. of sulfuric acid in 10 ml. of water. Solid sodium bicarbonate was added to neutralize all acid and the mixture evaporated to dryness *in vacuo*. Leaching of the residue with hot chloroform, subsequent evaporation and trituration with ether gave 0.26 g. of crude crystalline eneone amide (yield 68%). After sublimation at 120–130° (0.001 mm.) and crystallization from benzene–chloroform, a pure product was obtained, m.p. 120–122°, showing no depression of a mixed melting point with the specimen obtained from the ene-one acid (below).

(b) A solution of 10.5 g. (0.075 mole) of 3-keto-4-cyclohexenecarboxylic acid[20] (XXXIV) in 240 ml. of a 1:1 mixture of dry dioxane and dry tetrahydrofuran was cooled to −4° in a salt–ice-bath. With rapid stirring, 8.0 g. (0.079 mole) of triethylamine was added, followed after 15 min. by 7.5 g. (0.079 mole) of methyl chlorocarbonate. The reaction mixture was stirred at −4° for 90 min. and then a slow stream of ammonia was bubbled into the solution for 5 min. After stirring for a further 15 min. the mixture was filtered and the filtrate concentrated *in vacuo* to give 10.5 g. of a yellow, viscous oil. Crystallization from chloroform–benzene produced 3.4 g. (35% yield) of material, m.p. 117–121°. Repeated crystallization of a sample for analysis gave the pure product, m.p. 122–123°, ultraviolet λ_{max} 221 mμ (log ε 3.83) in ethanol.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.40; H, 6.52; N, 10.07. Found: C, 60.55; H, 6.57; N, 10.08.

1,4-Dihydro-3,5-dimethoxybenzylamine (XXXV).—To a suspension of 10.0 g. (0.26 mole) of lithium aluminum hydride in 500 ml. of dry tetrahydrofuran was added 20.3 g. (0.11 mole) of 1,4-dihydro-3,5-dimethoxybenzamide (XXX). After refluxing for 6 hr. and stirring at room temperature for an additional 15 hr., 50 ml. of water was added cautiously with cooling in ice. The slurry was then filtered, the residue suspended in 300 ml. of methylene chloride and filtered again. After drying the combined filtrates over anhydrous magnesium sulfate and evaporation of the solvents, a crude oil was obtained which, on distillation from an oil-jacketed flask, b.p. 130° (0.005 mm.), jacket temperature, gave 15.2 g. of a mixture of the benzylamine and dihydrobenzylamine; ultraviolet λ_{max} mμ (log ε): 224 (3.65), 275 (2.99), 281 (2.99), in ethanol.

3,5-Dimethoxybenzylamine, b.p. 94–96° (0.1 mm.), prepared by an analogous procedure (yield 70%) from 3,5-dimethoxybenzamide, gave an ultraviolet spectrum λ_{max} mμ (log ε): 225 (3.85), 275 (3.23), 281 (3.23), in ethanol. Thus the yield of dihydrobenzylamine can be estimated at 37–42% with the benzylamine formed in 63–58% yield (λ_{max} 225 and 275, 281 mμ). This is substantiated by isolation of the aromatic compound in 59% yield in the bromination experiment below.

Preparation of a 2,4-dinitrophenyl derivative with 2,4-dinitrofluorobenzene, in the usual way, led to a mixture of compounds, m.p. 112–125°, from which only the derivative of 3,5-dimethoxybenzylamine, m.p. 134–135°, could be isolated by fractional crystallization from methylene chloride–ethanol.

Anal. Calcd. for $C_{15}H_{15}N_3O_6$: C, 54.08; H, 4.54; N, 12.61. Found: C, 53.88; H, 4.61; N, 12.75.

4-Bromo-3,5-diketo-1-aminomethylcyclohexane (XXXVI).—A solution of 10.6 g. of the mixture of 1,4-dihydro-3,5-dimethoxybenzylamine (XXXV) and 3,5-dimethoxybenzylamine, obtained above, in 36 ml. of 3% hydrochloric acid, was heated on a steam-bath for 15 min. After cooling, the solution was made strongly alkaline with sodium hydroxide and extracted thoroughly with ether. The extracts, after washing with water, drying over magnesium sulfate and evaporation gave 6.2 g. of 3,5-dimethoxybenzylamine (59% yield). The aqueous solution was acidified with concentrated hydrochloric acid, cooled in ice and 4.2 g. (0.026 mole) of bromine added dropwise with rapid stirring. Adjustment to *p*H 6 with sodium carbonate solution induced crystallization of 3.1 g. of white crystalline product, m.p. 180°, 54% yield based on a maximum of 4.4 g. (0.026 mole) of the dienol ether XXXV in the original mixture. A sample was recrystallized from aqueous dioxane, m.p. 180°; isoelectric point: 5.7–6.9; ultraviolet absorption λ_{max} mμ (log ε): shld. 246 (3.21), 291 (4.29) in water; 230 (4.20), 273 (4.14), in 0.1 *N* HCl; plat. 231 (3.90), 289 (4.30), in 0.1 *N* NaOH; infrared absorption: 3160–3180, 1610 med., 1590 str., 1560 str. cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_7H_{10}BrNO_2$: C, 38.19; H, 4.58; N, 6.37; Br, 36.31. Found: C, 38.13; H, 4.61; N, 6.26; Br, 36.08.

4,4-Dibromo-3,5-diketo-1-aminomethylcyclohexane Hydrobromide (XXXVII).—To a solution of 0.10 g. (0.00045 mole) of the bromoamine XXXVI in 20 ml. of glacial acetic acid was added 9.0 ml. of 0.05 *N* (0.00045 mole) bromine in acetic acid. The colorless solution was concentrated *in vacuo* to 5 ml. Filtration of the crystals, which separated out at this point, gave 0.15 g., m.p. 139–140° dec.; recrystallized from acetic acid, m.p. 142° dec. (84% yield).

Anal. Calcd. for $C_7H_{10}Br_3NO_2$: C, 22.14; H, 2.65; N, 3.69; Br, 63.10. Found: C, 22.51; H, 2.87; N, 3.59; Br, 62.90.

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(24) J. S. Lumsden, *J. Chem. Soc.*, **87**, 90 (1905).