Summary

A method for the synthesis of α,β-unsaturated ethers is described and examples are given. This method appears to be quite general in its application.

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[CONTRIBUTION FROM THE EXPERIMENTAL RESEARCH LABORATORIES, BURROUGHS WELLCOME AND COMPANY]

MIXED BENZOINS.
III. THE STRUCTURE OF SOME UNSYMMETRICALLY SUBSTITUTED DESOXYBENZOINS

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RECEIVED JANUARY 22, 1931 PUBLISHED APRIL 6, 1931

In general, the structure of a mixed benzoin, when produced in the usual manner from two aldehydes, cannot be assigned with any degree of probability. The same remark applies to the desoxy compound derived from it by the usual methods of reduction, for even were the structure of the mixed benzoin known, the desoxy compound might be derived from it via the hydrobenzoin or the isohydrobenzoin, from which compounds water can be eliminated in several ways. Thus RCOCHOHR′ could give RCHOH-CHOHR′ which, by elimination of a molecule of water, could give either $RCOCH_2R'$ or RCH_2COR' by the "vinyl-dehydration" of Tiffeneau. Other compounds, for example, diphenylacetaldehydes, produced by the "pinacoline-dehydration" of Tiffeneau, might also be expected to occur. The authors therefore sought for an unambiguous reaction to prove the structure of desoxy compounds and selected for this purpose the Beckmann transformation. A given mixed benzoin, on reduction, can give two desoxy compounds, each of which can, in turn, give two oximes. With a suitable reagent these oximes are converted into amides, the amide being different in each case. The amides are readily identified, either by hydrolysis or by synthesis, so that it is possible to assign a structure to both the oxime and to the parent desoxy compound. Usually a mixed benzoin gives but one desoxy compound, but this is not general.[1] In turn a given desoxy compound yields usually only one oxime, but again this is not general, the authors having in one case obtained both oximes in sufficient amounts to carry out Beckmann transformations on them.

There appears to be only one instance recorded of the application of the Beckmann transformation to a desoxy type of compound,[2] in this case produced by a Friedel-Crafts reaction and of known structure. The present authors have applied the transformation to seven desoxy compounds

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[1] Jenkins, Buck and Bigelow, THIS JOURNAL, **52**, 4495 (1930).

[2] Cain, Simonsen and Smith, *J. Chem. Soc.*, **103**, 1035 (1913).

which were produced by the direct reduction of mixed benzoins, and have established the structure of these and of their oximes. The choice of the benzoins used was purely a matter of expediency, the most readily accessible ones being selected. The case of desoxydimethylaminobenzoin[1] was included in order to check the somewhat involved reasoning used in deducing its structure.

In a later paper it is hoped, after certain difficulties have been overcome, to apply the Beckmann transformation to the mixed benzoins themselves, since their structure cannot with certainty be inferred from the structure of the desoxy compounds.

Desoxy compounds of the mixed benzoins formed from the following pairs of aldehydes were investigated: (1) *o*-chlorobenzaldehyde and veratric aldehyde,[4] (2) *o*-chlorobenzaldehyde and anisaldehyde,[4] (3) *o*-chlorobenzaldehyde and *p*-dimethylaminobenzaldehyde,[3] (4) *o*-chlorobenzaldehyde and piperonal,[3] (5) benzaldehyde and anisaldehyde,[5] (6) benzaldehyde and piperonal,[3] and (7) benzaldehyde and *p*-dimethylaminobenzaldehyde.[1]

The desoxybenzoin from benzoin (1) gave 1-chlorophenylacet-3,4-dimethoxyanilide, and is hence 1-chlorobenzyl-3,4-dimethoxyphenyl ketone. Its oxime is the *syn*-dimethoxyphenyl derivative. The desoxy compound from benzoin (2) gave similarly 1-chlorophenylacetanisidide, showing that it is 1-chlorobenzyl-4-methoxyphenyl ketone and its oxime the *syn*-methoxyphenyl compound. From the desoxy compound of benzoin (3) 1-chlorophenylacet-4-dimethylaminoanilide was obtained and hence the desoxy compound is 1-chlorobenzyl-4-dimethylaminophenyl ketone and its oxime is the *syn*-dimethylaminophenyl oxime. The desoxy compound from benzoin (4) has an analogous structure, 1-chlorophenylacet-3,4-methylenedioxyanilide being formed on transformation of the oxime. The desoxy compound is therefore 1-chlorobenzyl-3,4-methylenedioxyphenyl ketone and the oxime is the *syn*-methylenedioxyphenyl compound.

From the desoxy compound of benzoin (5) two oximes were obtained. The *syn*-phenyl oxime gave 4-methoxyphenylacetanilide, while the *anti*-phenyl oxime gave benzoyl-4-methoxybenzylamine. Both these products indicate that the desoxybenzoin is 4-methoxybenzyl phenyl ketone. Tiffeneau and Orékhoff[6] have described a compound, prepared in a different manner, to which they assign the same structure. Their compound appears to be identical with that of the present authors. As a check of the

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[3] Buck and Ide, This Journal, **52**, 220 (1930).

[4] Buck and Ide, *ibid.*, **52**, 4107 (1930).

[5] Previously obtained by several workers. The preparation used was that of Kinney, *ibid.*, **51**, 1592 (1929).

[6] Tiffeneau and Orékhoff, *Bull. soc. chim.*, [4] **37**, 430, 1410 (1925).

method, benzyl-4-methoxyphenyl ketone was prepared by a Friedel–Craft reaction. From it only one oxime was obtained, and this was transformed into phenylacetanisidide, showing that the oxime had the *syn*-methoxyphenyl structure and confirming the method. As a further check, the last possible isomeric amide, 4-methoxybenzoylbenzylamine was prepared and found to differ from the other three amides obtained in the transformations. This series is shown in full below, to illustrate the reactions and the principles involved in this work.

Tiffeneau and Lévy[7] describe phenyl-3,4-methylenedioxybenzyl ketone, obtained by distilling the oxide of α-phenyl-β-3,4-methylenedioxyethylene. They give the melting point as 71–72°. The desoxy compound obtained by the present authors melts at 86° and its oxime, by the Beckmann transformation, gives phenylacet-3,4-methylenedioxyanilide, showing that the oxime is the *anti*-benzyl compound and that the desoxy compound is the isomer of Tiffeneau and Lévy's ketone and is benzyl-3,4-methylenedioxyphenyl ketone.

The structure of β-desoxy-*p*-dimethylaminobenzoin was earlier deduced by rather involved reasoning[2,8] and it was desirable to check this. The oxime gave phenylacet-4-dimethylaminoanilide and hence the β-desoxy compound is benzyl-4-dimethylaminophenyl ketone, as previously stated, and the oxime is the *anti*-benzyl oxime.

The yields of the desoxy compounds are frequently mediocre. It is quite possible that the isomeric desoxy compound and the diphenylacetaldehyde were present in some cases, but no serious attempt to isolate these was made, for the present purpose.

A few of the amides encountered hydrolyzed under rather drastic treatment. The acid fragment was readily isolated, but the basic fragment was degraded by the reagent used. This is to be expected with amines such as dimethyl-*p*-phenylenediamine.[9] For this reason the structure of the amide was checked synthetically in all cases. For practical purposes the identification of the acid fragment is sufficient. The majority of the amides resisted hydrolysis even by powerful reagents.

The authors have avoided assigning definite names to the mixed benzoins (*cf.* Buck and Ide[3]) on account of the ambiguity in their structure. It is hoped to clear up this point soon.

The structures of the desoxy compounds and of their oximes have been deduced on the assumption that the transformation takes place directly, between the vicinal groups of the oximes, and that no transposition of groups, such as that suggested by Meisenheimer[10] for the benzil oximes,

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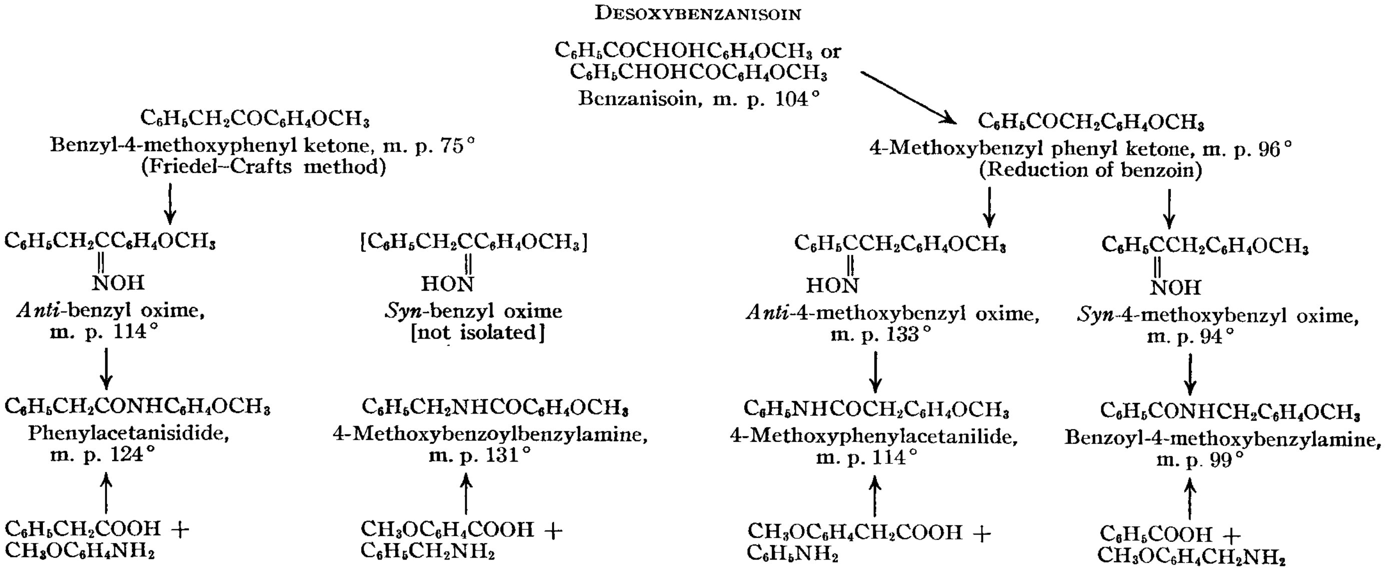
[7] Tiffeneau and Lévy, *Compt. rend.*, **190**, 1510 (1930).

[8] Jenkins, Bigelow and Buck, THIS JOURNAL, **52**, 5198 (1930).

[9] *Cf.* Merz, Weith and Weber, *Ber.*, **10**, 762 (1877).

[10] Meisenheimer, *ibid.*, **54**, 3206 (1921).


DESOXYBENZANISOIN
$C_6H_5COCHOHC_6H_4OCH_3$ or
$C_6H_5CHOHCOC_6H_4OCH_3$
Benzanisoin, m. p. 104°
$C_6H_5CH_2COC_6H_4OCH_3$
Benzyl-4-methoxyphenyl ketone, m. p. 75°
(Friedel–Crafts method)
$C_6H_5COCH_2C_6H_4OCH_3$
4-Methoxybenzyl phenyl ketone, m. p. 96°
(Reduction of benzoin)
$C_6H_5CH_2\underset{\text{NOH}}{\underset{\|}{C}}C_6H_4OCH_3$
Anti-benzyl oxime,
m. p. 114°
$[C_6H_5CH_2\underset{\text{HON}}{\underset{\|}{C}}C_6H_4OCH_3]$
Syn-benzyl oxime
[not isolated]
$C_6H_5\underset{\text{HON}}{\underset{\|}{C}}CH_2C_6H_4OCH_3$
Anti-4-methoxybenzyl oxime,
m. p. 133°
$C_6H_5\underset{\text{NOH}}{\underset{\|}{C}}CH_2C_6H_4OCH_3$
Syn-4-methoxybenzyl oxime,
m. p. 94°
$C_6H_5CH_2CONHC_6H_4OCH_3$
Phenylacetanisidide,
m. p. 124°
$C_6H_5CH_2NHCOC_6H_4OCH_3$
4-Methoxybenzoylbenzylamine,
m. p. 131°
$C_6H_5NHCOCH_2C_6H_4OCH_3$
4-Methoxyphenylacetanilide,
m. p. 114°
$C_6H_5CONHCH_2C_6H_4OCH_3$
Benzoyl-4-methoxybenzylamine,
m. p. 99°
$C_6H_5CH_2COOH +$
$CH_3OC_6H_4NH_2$
$CH_3OC_6H_4COOH +$
$C_6H_5CH_2NH_2$
$CH_3OC_6H_4CH_2COOH +$
$C_6H_5NH_2$
$C_6H_5COOH +$
$CH_3OC_6H_4CH_2NH_2$

takes place. The amides actually obtained could not have been produced had a transposition of groups occurred. Further strong evidence in favor of the authors' assumption, is afforded by the fact that the oximes of several desoxy compounds whose structures have been established by other methods (*v. s.*) gave without exception the amides to be expected on the basis of a straight transformation between the vicinal groups.

TABLE I

KETONES

No.	Phenyl ketones	Formula	From benzoin	Yield, %
(A)[4]	1-Chlorobenzyl-3,4-dimethoxy-	$ClC_6H_4CH_2COC_6H_3(OMe)_2$	(1)	..
(B)[4]	1-Chlorobenzyl-4-methoxy-	$ClC_6H_4CH_2COC_6H_4OMe$	(2)	..
(C)	1-Chlorobenzyl-4-dimethylamino-	$ClC_6H_4CH_2COC_6H_4NMe_2$	(3)	44
(D)	1-Chlorobenzyl-3,4-methylenedioxy-	$ClC_6H_4CH_2COC_6H_3O_2CH_2$	(4)	96
(E)[6]	4-Methoxybenzyl	$MeOC_6H_4CH_2COC_6H_5$	(5)	87
(F)	Benzyl-4-methoxy-	$C_6H_5CH_2COC_6H_4OMe$	...	..
(G)	Benzyl-3,4-methylenedioxy-	$C_6H_5CH_2COC_6H_3O_2CH_2$	(6)	64
(H)[1]	Benzyl-4-dimethylamino-	$C_6H_5CH_2COC_6H_4NMe_2$	(7)	..

The ketones (with the exception of F) were prepared by reducing the benzoin by boiling with tin and concd. hydrochloric acid, in alcoholic solution, for six or more hours (Buck and Ide, Refs. 3 and 4). Ketone F was prepared by a Friedel–Crafts reaction on phenylacetyl chloride and anisole. Ketones A, B, E and H have been described elsewhere, A and B without structures assigned. Ketone E is reduced catalytically to a compound melting at 128.5°, probably the same as Tiffeneau and Orékhoff's compound of m. p. 134–135°.[6] By analogy, it is the hydrobenzoin. It forms silky, white leaves, giving an intense golden-brown color with concd. sulfuric acid (*cf.* (6) where the color is given as red). *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.73; H, 6.61. Found: C, 73.86; H, 6.77.

			Analyses, %					
			Calcd.			Found		
No.	M. p., °C.	Appearance	C	H	N	C	H	N
(C)	122	White needles	70.17	5.88	5.11	70.28	5.87	5.00
(D)	105	White cubes	65.55	4.03		65.87	4.06	
(F)	73	Pearly tables	79.60	6.24		79.58	6.31	
(G)	86	White prisms	74.96	5.37		74.70	5.42	

TABLE II

OXIMES

No.	Phenyl ketoximes	Formula	From ketone
(A)	*Anti*-1-chlorobenzyl-3,4-dimethoxy-	$ClC_6H_4CH_2C(=NOH)C_6H_3(OMe)_2$	A
(B)	*Anti*-1-chlorobenzyl-4-methoxy-	$ClC_6H_4CH_2C(=NOH)C_6H_4OMe$	B
(C)	*Anti*-1-chlorobenzyl-4-dimethylamino-	$ClC_6H_4CH_2C(=NOH)C_6H_4NMe_2$	C
(D)	*Anti*-1-chlorobenzyl-3,4-methylenedioxy-	$ClC_6H_4CH_2C(=NOH)C_6H_3O_2CH_2$	D
(E-1)	*Anti*-4-methoxybenzyl	$MeOC_6H_4CH_2C(=NOH)C_6H_5$	E
(E-2)	*Syn*-4-methoxybenzyl	$MeOC_6H_4CH_2(HON=)CC_6H_5$	E
(F)	*Anti*-benzyl-4-methoxy-	$C_6H_5CH_2C(=NOH)C_6H_4OMe$	F
(G)	*Anti*-benzyl-3,4-methylenedioxy-	$C_6H_5CH_2C(=NOH)C_6H_3O_2CH_2$	G
(H)	*Anti*-benzyl-4-dimethylamino-	$C_6H_5CH_2C(=NOH)C_6H_4NMe_2$	H

TABLE II (*Concluded*)

Two methods were used for preparing the oximes. [1] The ketone, in alcoholic solution, was allowed to stand with an excess of hydroxylamine acetate (from the hydrochloride and potassium acetate) and finally warmed for two hours and the mixture then diluted with water. [2] The ketone, in pyridine solution, was warmed on the bath for three hours with hydroxylamine hydrochloride (excess) and the mixture then diluted with water. In either case the product was recrystallized from alcohol until pure.

Oxime E-1 has been described by Tiffeneau and Orékhoff,[6] form undetermined.

Oxime H has been described by Jenkins, Buck and Bigelow,[1] form undetermined.

No.	Yield, %	M. p., °C.	Appearance	Preparation	Nitrogen analyses, % Calcd.	Found
(A)	64	137	Glittering prisms	[1]	4.58	4.78
(B)	86	97	Dull crystals	[1] [2]	5.07	5.07
(C)	61	173	Glittering prisms	[1]	9.70	9 83
(D)	42	120	Glittering rhombs	[1]	4.83	4.72
(E-1)	23	133	....	[1]	..	..
(E-2)	19	94	Felted needles	[1]	5.80	5.97
(F)	94	114	Glittering crystals	[2]	5.80	5.84
(G)	60	103	Tiny needles	[2]	5.48	5.61

Oxime G was accompanied by very small amounts of a second oxime, which formed thick, white prisms, melting at 130°. *Anal.* Calcd. for $C_{15}H_{13}O_3N$: N, 5.48. Found: N, 5.45.

TABLE III

AMIDES

No.	Name	Formula	From oxime
(A)	1-Chlorophenylacet-3,4-dimethoxyanilide	$ClC_6H_4CH_2CONHC_6H_3(OMe)_2$	A
(B)	1-Chlorophenylacetanisidide	$ClC_6H_4CH_2CONHC_6H_4OMe$	B
(C)	1-Chlorophenylacet-4-dimethylaminoanilide	$ClC_6H_4CH_2CONHC_6H_4NMe_2$	C
(D)	1-Chlorophenylacet-3,4-methylenedioxyanilide	$ClC_6H_4CH_2CONHC_6H_3O_2CH_2$	D
(E-1)	4-Methoxyphenylacetanilide	$MeOC_6H_4CH_2CONHC_6H_5$	E-1
(E-2)	Benzoyl-4-methoxybenzylamine	$C_6H_5CONHCH_2C_6H_4OMe$	E-2
(F)	Phenylacetanisidide	$C_6H_5CH_2CONHC_6H_4OMe$	F
(G)	Phenylacet-3,4-methylenedioxyanilide	$C_6H_5CH_2CONHC_6H_3O_2CH_2$	G
(H)	Phenylacet-4-dimethylaminoanilide	$C_6H_5CH_2CONHC_6H_4NMe_2$	H
(I)	4-Methoxybenzoylbenzylamine	$C_6H_5CH_2NHCOC_6H_4OMe$	...

The amides were synthesized by one of the following two methods, the one used being determined by circumstances: (1) the Schotten–Baumann reaction, (2) heating the acid and amine together in molecular proportions, at 180–200° for two hours.

The Beckmann reaction was carried out in one or both of two ways, (1) by means of benzenesulfone chloride and sodium hydroxide solution, after the manner of a Schotten–Baumann reaction, and (2) by the action of phosphorus pentachloride on the oxime in absolute ether. The first method is convenient, rapid and gives good yields.

Amides A, C and D were hydrolyzed by strong acids, giving *o*-chlorophenylacetic acid.

TABLE III (*Concluded*)

No.	Synth. prep.	Beckmann	M. p., °C.	Appearance	Nitrogen analyses, % Calcd.	Found	Refs.
(A)	2	2	177	White, slender needles	4.58	4.68	11,12
(B)	2	1	163	Glittering needles	5.07	5.23	
(C)	1	2	165	White prisms	9.70	9.88	
(D)	1	1, 2	175	Dull, white needles	4.83	4.98	13
(E-1)	2	2	113	Buff, slender prisms	5.80	5.72	
(E-2)	1	1	96	Faint yellow plates	5.80	5.89	14
(F)	2	1	121	Glittering crystals	5.80	5.89	
(G)	1	1	146	Buff, pearly plates	5.48	5.65	
(H)	1	1	144	Cream, slender prisms	11.02	10.97	
(I)	2	..	131	White, flaky crystals	5.80	5.98	15

The solubilities of the compounds described are not distinctive. The amides are moderately soluble in alcohol, and rather soluble in benzene, chloroform, etc. The oximes are frequently very soluble in absolute alcohol, but separate readily on the addition of a little water. In every instance the compounds were recrystallized from alcohol until pure. The melting points given are corrected. The identification of the amides obtained in the Beckmann reaction was always carried out by comparison and mixed melting point determinations with a synthetic specimen. The analyses are all microanalyses (Pregl).

Summary

The Beckmann transformation has been used to determine the structures of certain unsymmetrically substituted desoxybenzoins, and to assign configurations to the oximes derived from them. Seven desoxy compounds were examined. A number of new desoxy compounds, oximes and amides are described. The results support the view that the transformation takes place between the vicinal groups of the oximes.

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[11] Preparation of Mehner, *J. prakt. Chem.*, [2] **62,** 556 (1900). [12] 4-Aminoveratrole is conveniently prepared by a method analogous to that of Rupe and Majewski,[13] from veratric oxime, via veratronitrile and veratric amide, upon which a Hofmann reaction is carried out, using the theoretical amount of sodium hypochlorite. [13] Aminopiperole is best prepared by the method of Rupe and Majewski, *Ber.*, **33,** 3401 (1900). The preparation is much improved by using the theoretical amount of sodium hypochlorite in the last stage. Special treatment of the amide is then not necessary. [14] 4-Methoxybenzylamine is readily prepared by the method of Goldschmidt and Polonowska, *Ber.*, **20,** 2407 (1887). [15] Obtained by Beckmann [*Ber.*, **37,** 4138 (1904)] by the action of benzenesulfone chloride on N-benzylanisaldoxime, and also mentioned by Rügheimer, *Ber.* **49,** 592 (1916).