creosol benzenesulfonates (m.p. 50–71°). This procedure was repeated two additional times; the melting ranges for the mixtures were: (a) 50–71°, (b) 49–68° and (c) 49.5–59°.

Anal. Calcd. for $C_{14}H_{14}O_4S$: C, 60.42; H, 5.07. Found: C, 60.52; H, 5.37.

Pure creosol benzenesulfonate (m.p. 65–66.5°) and pure isocreosol benzenesulfonate (m.p. 88–89°)[14] were prepared and a mixed melting point diagram was made up from known mixtures of the pure components. The melting points of the mixtures of sulfonates obtained from VIII (a, b, c above), correspond to mixtures of creosol and isocreosol benzenesulfonates in the ratios 45:55, 48:52 and 56:44, respectively.

(14) Isocreosol, b.p. 112° (23 mm.), was prepared from *p*-toluidine, by modifications of the procedure previously reported by M. O. DeVries, *Rec. trav. chim.*, **28**, 289 (1909). Isocreosol benzenesulfonate was prepared by standard procedures from isocreosol, and recrystallized to constant melting point (m.p. 88–89°) from alcohol-water. A Von Wacek and A. Von Beyard, *Ber.*, **74B**, 845 (1941), report the melting point of isocreosol benzenesulfonate to be 94°.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

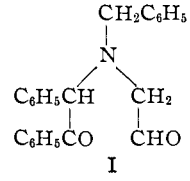
Ring–Chain Relationships in the 2-(N-Acetal-N-benzylamino)-1,2-diphenylethanone and Ethanol Series[1]

BY ROBERT E. LUTZ AND CLAIBOURNE E. GRIFFIN

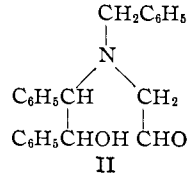
RECEIVED MARCH 29, 1954

N-Acetal-N-benzylamino-1,2-diphenylethanone and the two stereoisomeric ethanols have been prepared; their structures were shown by ultraviolet absorptions and by reduction of the former to one of the latter by aluminum isopropoxide. Hydrolyses gave corresponding dihydroxy and monohydroxy-morpholines by irreversible cyclization through the aldehyde group; the cyclic structures were shown by ultraviolet absorptions and by reduction characteristics. Acid-catalyzed etherifications and transetherifications of both open-chain and cyclic compounds were easily effected in absolute alcohols. A small amount of water was necessary to effect cyclizations under these conditions, however; and this is explained in terms of hydrolysis first to the hemiacetal or free aldehyde. Dehydration of the dihydroxymorpholine gave irreversibly a hydroxydihydrooxazine, the structure of which was shown by its stilbene type ultraviolet absorptivity. Lithium aluminum hydride reduction proceeded one stage to an enolate-alkoxide which only upon subsequent hydrolysis gave the then further reducible 2-hydroxymorpholine.

This investigation deals with the two β,β'-dioxygenated amines I and II which have been obtained only in the open-chain or cyclic acetal or cyclic hemiacetal forms; it is a part of the study of the

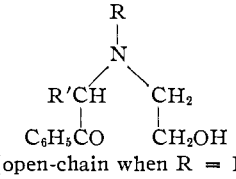


I

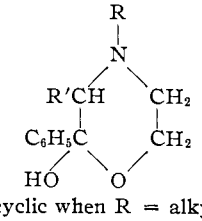


II

effect of structural modifications of certain types of amino alcohol and amino ketone systems on pharmacological activity and on the ring-chain relationships of the type III–IV[2]; and it is essentially an



(open-chain when R = H)
III



(cyclic when R = alkyl)
IV

extension of early and limited work on diacetalamine[3] and acetalethanolamine[4] which have been converted into the cyclic acetal-ketal and the cyclic acetal of types IX and XXII, respectively.

In preliminary experiments in this field[5] α-(N-benzyl-N-acetalamino)-acetophenone was obtained as an unstable hydrochloride V. The N-benzyl-

$$C_6H_5COCH_2N(CH_2C_6H_5)CH_2CH(OC_2H_5)_2\cdot HCl \quad V$$

1,2-diphenyl series, however, was chosen for the first extended study because of the greater stability and good melting points of the compounds involved, for the structural analogy to the previously studied 1,2-diphenylamino alcohols and hydroxymorpholines III–IV, and in order to obtain new pharmacologically interesting compounds in this series in which there has been found a high incidence of necrotizing activity against mammalian tumors.[6]

2-(N-2,2-Diethoxyethyl-N-benzylamino)-1,2-diphenylethanone (VIIIa) which is related to I, was obtained in good yield by direct condensation of desyl chloride VI with α-benzylaminoacetal (VII); the hydrogen chloride liberated was removed as the hydrochloride of the reagent VII which was used in sufficient excess for the purpose. Transetherification of this diethylacetal VIIIa to and from the corresponding dimethylacetal VIIIb without cyclization was readily accomplished by the action of the appropriate absolute alcohol and hydrogen chloride.

That these compounds VIIIa and b are open-chain as written was demonstrated as follows: the ultraviolet molecular absorptivities in the 240–250 mμ region (ϵ 12.4–12.7 $\times$ 10^3) are of the character-

(1) This investigation was supported by a grant from the Eli Lilly Company.

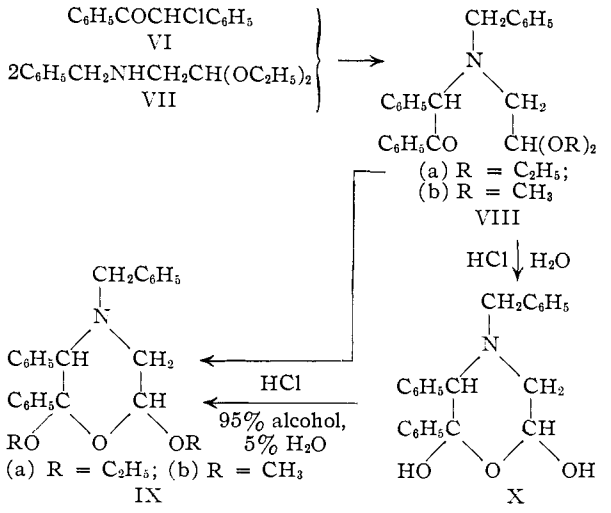
(2) *Cf.* (a) R. E. Lutz, J. A. Freek and R. S. Murphey, THIS JOURNAL, **70**, 2015 (1948); (b) R. E. Lutz and R. H. Jordan, *ibid.*, **71**, 996 (1949).

(3) L. Wolff, *Ber.*, **21**, 1481 (1888); L. Wolff and R. Marburg, *Ann.*, **363**, 169 (1908).

(4) L. Knorr, *Ber.*, **32**, 729 (1899).

(5) Carried out in this Laboratory by Dr. R. H. Jordan.

(6) *Cf.* (a) J. L. Hartwell and S. R. L. Kornberg, THIS JOURNAL, **67**, 1606 (1945); (b) J. L. Hartwell and M. J. Shear, Am. Assoc. Cancer Research, 38th meeting, May 16–17, 1947 (*cf. Cancer Research*, **7**, 716 (1947)); (c) M. J. Shear, V. Downing, J. L. Hartwell, *et al.*, Am. Assoc. Cancer Research, 40th meeting, April 16–17, 1949 (*cf. Cancer Research*, **9**, 625 (1949)).



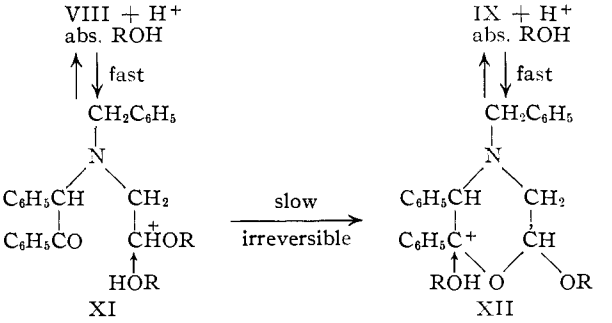
istic magnitudes for a benzoyl group, and are similar to those of desoxybenzoin and its α-diethylamino derivative[2b]; and the carbonyl-specific reagent aluminum isopropoxide easily reduces the compound to the corresponding acetalamino alcohol XIX. When either the open-chain acetal VIIIa or b was hydrolyzed with aqueous acid, the aldehydo-amino-ketone I was obtained in the form of the cyclic hydrate X which is a cyclic hemiacetal-hemiketal (a 2,6-dihydroxymorpholine). The cyclic nature of this product was demonstrated by the lack of significant ultraviolet absorptivity in the region characteristic for a benzoyl group, and by non-reduction under standard conditions by aluminum isopropoxide. When the more powerful reducing agent lithium aluminum hydride was used, reduction then proceeded readily with characteristic attack at both the hemiacetal and hemiketal groups to give the ethanolamino alcohol XVIII, a reduction which is analogous to the reduction of the mono-hemiketal system of numerous other hydroxymorpholines IV which have been studied.[7]

Acid-catalyzed etherifications of the dihydroxymorpholine X can be accomplished readily by the action of the appropriate alcoholic hydrogen chloride; but only the cyclic acetal-ketals IXa and b were obtained, and these were interconvertible under conditions which are standard for acid-catalyzed transetherifications, namely, hydrogen chloride and the appropriate absolute or 95% alcohol.

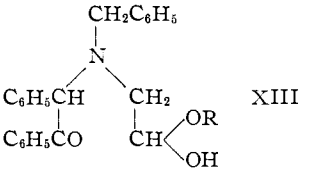
These same cyclic acetal-ketals IXa and b were obtained directly from the open-chain acetals VIIIa and b under transetherification conditions using hydrogen chloride and the appropriate alcohol containing, however, 5% of water; this acid-catalyzed cyclization does not go readily in anhydrous alcohol (treatment for 84 hours resulted in a yield of 6% of the cyclic acetal-ketal IXb).

The cyclic nature of these products IXa and b and the absence of a free benzoyl group was demonstrated by the lack of ultraviolet absorptivities characteristic of a benzoyl group and by the failure of the compounds to undergo reduction under the usual conditions by the carbonyl-specific reagents aluminum isopropoxide or lithium aluminum hydride. No conditions were discovered for accomplishing the rearrangement of any of the cyclic compounds IX or X under etherification or transetherification conditions into the open-chain compounds VIIIa or b. The cyclizations thus are irreversible and the cyclic forms are inherently the more stable.

A mechanism for cyclizations during acid-catalyzed transetherifications of the open-chain acetals must account for the requirement of a small but significant amount of water and may be expressed in the following terms: The etherifications and transetherifications of both open-chain and cyclic compounds VIII and IX in absolute alcohol would presumably involve extremely short-lived intermediate carbonium ions such as XI and XII which would be present in very low concentrations. The cyclization of the open-chain ion XI to XII



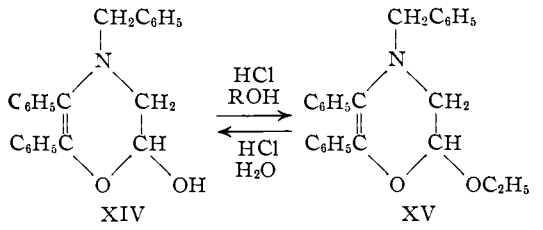
would be slow because of dependency upon speed of contortion of the chain into a conformation favorable for ring closure,[8] whereas solvent molecules are present in large concentration and could react much more rapidly to regenerate an open-chain acetal VIII. When a small amount of water is present partial hydrolysis of the open-chain acetal VIII to the open-chain hemiacetal XIII (R = alkyl), the aldehyde hydrate (XIII, R = H), and/or the aldehyde itself (I), would undoubtedly occur to a significant extent; and any one of these intermediates would be relatively long-lived as compared with the ion XI and could conceivably then be involved in a reasonably rapid cyclization.



N-Benzyl-2-hydroxy-5,6-diphenyl-2,3-dihydro-1,4-oxazine (XIV) was obtained by the action of hot concentrated hydrochloric acid on the dihydroxymorpholine X, a reaction analogous to the dehydration of monohydroxymorpholines of the type IV where R = alkyl. This compound XIV structurally is a cyclic enol-hemiacetal of the parent compound I, and at the same time it is a typical stilbene and shows characteristic ultraviolet absorptivity. As a cyclic hemiacetal it can readily be etherified under acid catalysis to the cyclic acetal XV, and this acetal in turn can be transetherified and can be hydro-

(7) (a) W. L. Truett; (b) J. W. Baker; (c) R. L. Wayland, Dissertations, University of Virginia; 1951, 1952, 1952.

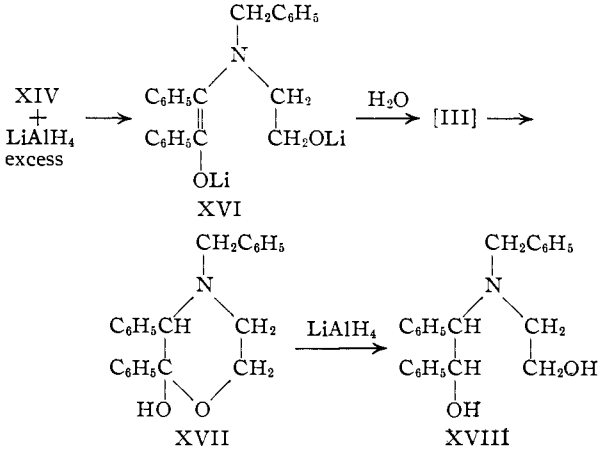
(8) Cyclization by acid-catalyzed intramolecular reaction between an acetal oxygen at the carbon of the protonated ketone carbonyl of VIII would be unlikely because the fixing of the cyclic structure in such a scheme would require the separation of a positive alkyl ion,



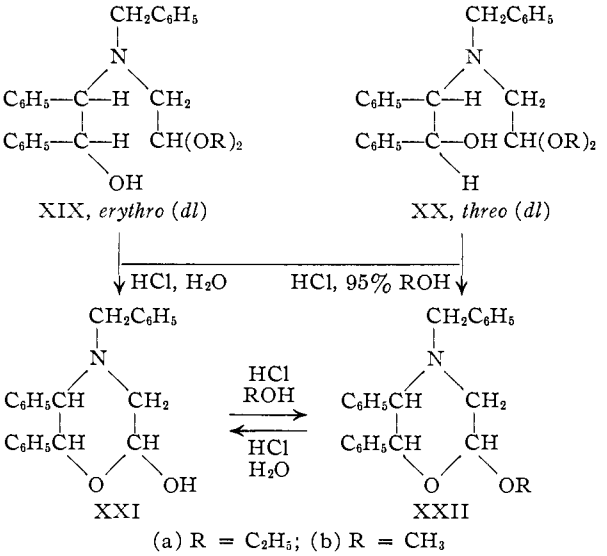
XIV XV

lyzed back to the cyclic hemiacetal XIV. Like its analog obtained by dehydration of IV (R = alkyl, R′ = phenyl) it could not be reconverted by acid-catalyzed addition of water or alcohols to the dihydroxy or dialkoxymorpholines X or IX, a fact which attests to the marked resonance stabilization involved in the stilbene system. This stability is to be contrasted with the greater reactivity of the styrene analogs made by dehydration of IV (R = alkyl, R′ = H) which readily undergo acid-catalyzed conversion back to cyclic hemiketals IV or to corresponding cyclic ketals.

As also would be expected of a cyclic hemiacetal, the hydroxydihydro-oxazine XIV, but not its ether XV, proved to be reducible by means of an excess of lithium aluminum hydride. However, subsequent hydrolysis of the reaction mixture, which first destroyed the excess of reducing agent, gave the hydroxymorpholine XVII (known) which has its hydroxyl group on the phenylated side of the morpholine ring; this compound is itself still a cyclic hemiacetal and is in fact reducible to the dialcohol XVIII when once isolated and subjected to further reduction by lithium aluminum hydride.[7c] The over-all result has been the equivalent of reducing selectively the aldehyde group of I; however, in this one-stage reduction the product isolated XVII obviously cannot have been present as such in the reduction mixture and it must therefore have been present in some combined form, presumably the enolate-alkoxide XVI in which the potential ketone III or cyclic hemiketal system XVII is protected against further attack by reducing agent.[9] The reduction can be formulated either in terms of nucleophilic reductive displacement-cleavage[10] at the enol ether bridge bond of XIV or in terms of formation first of the ketone-enolate ion of I followed by normal and rapid reduction of the aldehyde group thus liberated.



The *erythro* and *threo* 2-N-[(2,2-diethoxyethyl)-N-benzylamino]-1,2-diphenylethanols XIX and XX are representative of the parent structure II which is structurally isomeric with the ethanolamino ketones of the type III. The compound II was obtained only in the one cyclic hemiacetal form XXI although diastereoisomers related to XIX and XX might have been expected.



(a) R = C_2H_5; (b) R = CH_3

The *erythro* compound XIX was prepared by condensation of benzylamino acetal VII and *erythro*-stilbene chlorohydrin, and the *threo* isomer XX by condensation with *cis*-stilbene oxide; the configurations were assigned on the basis of the known mode of inversion–cleavage of oxides by ammonia and amines.[2a,11] The *erythro* isomer XIX was obtained also by reduction of the acetalamino ketone VIIIa with the ketone-specific reagents, aluminum isopropoxide or lithium aluminum hydride; the assignment of configurations thus finds further support in that the predominance of this particular stereochemical mode of reduction is consistent with both fact and prediction in many analogous cases.[12]

The hydrochloric acid hydrolysis of the two acetalamino alcohols XIX and XX gave one and the same product which proved to be the cyclic-hemiacetal XXI; the stereo-configurational differences between XIX and XX did not survive the reaction[13] and the configuration of this product is unknown. The cyclic-hemiacetal formulation XXI was demonstrated by the following facts: the compound resists reduction by the carbonyl-specific reagent aluminum isopropoxide (in contrast with the easily reduced open-chain acetalamino ketone VIII); it is reduced with typical facility by lithium aluminum hydride to the diethanolamine XVIII; and

(9) *Cf.* R. E. Lutz and J. S. Gillespie, Jr., THIS JOURNAL, **72**, 2002 (1950).

(10) (a) *Cf.* Discussion of mechanism of lithium aluminum hydride reduction, W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 479; (b) see also ref. 7c.

(11) (a) F. H. Dickey, W. Fickett and H. J. Lucas, THIS JOURNAL, **74**, 944 (1952); (b) G. K. Helmkamp and H. J. Lucas, *ibid.*, **74**, 951 (1952).

(12) *Cf.* D. J. Cram and F. A. A. Elhafez, *ibid.*, **74**, 5828 (1952).

(13) In the dehydration of diethanolamines of the type XVIII to morpholines, similar stereoisomerization has been observed (*cf.* ref. 7b),

it shows a typical infrared absorption band for the hydroxyl group (2.74 μ) and no carbonyl band in the 6μ region.

Hydrogen chloride in absolute or 95% alcohol causes ready etherification of the cyclic hemiacetal XXI to the cyclic methyl or ethyl ethers XXII, which are acetals and can be interconverted by transetherification.

The two open-chain acetalamino alcohols XIX and XX (in contrast with VIII) have an available alcoholic hydroxyl group within the molecule and should theoretically be capable of undergoing intramolecular cyclo-transetherification under the influence of hydrogen chloride; however, when anhydrous alcohols are used as the solvent (as in the case of the acetalamino ketone VIII) they undergo ready transetherification without significant cyclization or stereoisomerization during the process. The cyclic acetals XXII can be obtained by cyclization of either of the open-chain acetals XIX or XX under acid-catalyzed alcoholysis providing 95% rather than absolute alcohol is used; here also stereoconfigurational differences existing in the open-chain compounds have been lost in going to the cyclic compounds, and the configuration of the cyclic compound is not known. Acid hydrolysis of the cyclic acetals regenerates the cyclic hemiacetal XXI. Cyclization thus appears to be irreversible (as is the case with compounds of the type III–IV and VIII–IX) in spite of a certain degree of pressure toward ring-opening which would be associated with the utilization of a second molecule of alcohol in going from XXII to the open-chain acetal.

The mechanism of cyclization offered here to account for the role of water is similar to that postulated for the analogous cyclization of VIII. It may be assumed that the ion (analogous to XI) formed at the acetal group by protonation and loss of alcohol must also be too short-lived to allow the conformational change necessary for cyclization to proceed at a reasonable rate, that this ion reacts much more rapidly with solvent to give the acetal XIX or XX (a or b), but that in the presence of 5% of water equilibrium amounts of free or protonated aldehyde (II) would be formed with sufficient life and reactivity for cyclization. Stereoisomerization does not appear to occur first by direct ionization at the carbinol carbon of XIX or XX because these open-chain compounds retain their configurations during transetherification, and it is not explained; however, the postulated mechanism does not appear to be incompatible with this fact.[14]

The striking effect of small amounts of water here in promoting and catalyzing the cyclizations suggests numerous applications and some of these are being investigated, for example, the cyclization of the open-chain acetal of glucose, and the cyclization or fission rearrangements between various open-chain and cyclic esters of gamma and ortho ketonic acids and aldehyde acids.

Acknowledgment.—This research was supported by a generous grant from the Eli Lilly Company. The Lilly Research Laboratories have carried out hypnotic, anticonvulsant, local anesthetic, hypertension and chemotherapy tests on the principal compounds reported in this paper and found no interest in the activities.

Preliminary work in the field was initiated by Dr. R. H. Jordan under a grant-in-aid from the National Institutes of Health.

Experimental[15]

The preparation of α-N-benzylaminoacetal (VII)[16] was modified as follows.

A solution of 39.4 g. (0.2 mole) of bromoacetal and 50.3 g. (0.5 mole) of benzylamine in 300 ml. of absolute ethanol was

TABLE I

CATALYZED SYNTHESES AND INTERCONVERSIONS

Product[a]	Reactant	Reaction medium[b]	Yield, %	Reaction time, hr.	Method of prep.[c]
VIIIa	VIIIb	Abs. MeOH	79	2	A
VIIIb	VIIIa	Abs. EtOH	76	2	A
X·HCl	VIIIa	H_2O	56	3	B
	VIIIb	H_2O	59	3	B
X	IXa	H_2O	74	1	C[d]
	IXb	H_2O	70	1	C[d]
IXa	VIIIa	95% EtOH	45	2	A
	VIIIb	95% EtOH	52	2	A
	IXb	Abs. EtOH	72	2	A
	IXb	95% EtOH	71	2	A
	X	Abs. EtOH	67	3	A
	X	95% EtOH	70	2	A
IXb	VIIIa	95% MeOH	53	2	D
	VIIIb	95% MeOH	57	2	D
	IXa	Abs. MeOH	65	2	D
	IXa	95% MeOH	63	2	D
	X	Abs. MeOH	61	2.5	D
	X	95% MeOH	54	2.5	D
XIV	XV	H_2O	67	1	C[d]
XV	XIV	Abs. EtOH	47	2	C
XIXa	XIXa	Abs. EtOH	73	2	A
	XIXb	Abs. MeOH	58	2	A
XXa	XXa	Abs. EtOH	75	2	A
	XXb	Abs. MeOH	64	2	A
XXI	XIXa	H_2O	68	2	A
	XXa	H_2O	71	2	A
	XXIIa	H_2O	87	1	A[d]
	XXIIa	H_2O	83	1	A[d]
XXIIa	XIXa	95% EtOH	65	2	A
	XXa	95% EtOH	52	4	A
	XXI	Abs. EtOH	56	3	A
	XXI	95% EtOH	63	3	A
XXIIb	XIXa	95% MeOH	79	2	A
	XXa	95% MeOH	62	4	A
	XXI	Abs. MeOH	71	3	A
	XXI	95% MeOH	79	3	A

[a] See Table II and experimental section for analyses. [b] MeOH = CH_3OH; EtOH = C_2H_5OH. [c] See descriptions in experimental section. [d] In these five reactions the reaction mixture was not refluxed but was held at 70° for one hour.

(14) Possibly water is more effective than alcohol in stereoisomerization; or the unknown and more strained ring configuration of XXII or XXI might undergo stereoisomerization more easily than the open-chain compounds XIX and XX. There is also the remote possibility that under the unique drive for ring closure the carbinol hydroxyl of XIX or XX might undergo incipient ionization and take part in intramolecular solvolytic displacement by the hemiacetal or aldehyde hydrate hydroxyl with accompanying stereoisomerization to produce the less strained arrangement.

(15) (a) All melting points are "corrected"; (b) microanalyses were performed by Mrs. Carolyn Jeffries, Miss Patricia Paynter and the Clark Microanalytical Laboratory.

(16) I. A. Kaye and I. Minsky, THIS JOURNAL, **71**, 2272 (1949).

TABLE II

HYDROLYSIS AND ALCOHOLYSIS PRODUCTS[a]

Compound	Crystallized from[b]	M.p., °C.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
VIIIb	Pet. ether	116–117[f]	$C_{25}H_{27}NO_3$[c]	77.09	76.83	6.99	6.90
IXa	Pet. ether	186–187[f]	$C_{27}H_{31}NO_3$[d]	77.66	77.50	7.48	7.31
IXa·HCl	EtOH–Et_2O	223–224	$C_{27}H_{31}NO_3$·HCl	71.43	71.20	7.10	6.82
IXb	50% MeOH	191–192[f]	$C_{25}H_{27}NO_3$	77.09	77.01	6.99	6.85
IXb·HCl	EtOH–Et_2O	210–211	$C_{25}H_{27}NO_3$·HCl	70.49	70.21	6.63	6.54
X	CH_3COOEt	214–215[f]	$C_{23}H_{23}NO_3$	76.43	76.20	6.41	6.28
X·HCl	MeOH–but.	243–245	$C_{23}H_{23}NO_3$·HCl	69.42	69.67	6.08	6.00
XV[g]	Isoöctane	101–102	$C_{25}H_{25}NO_2$	80.83	80.60	6.78	6.95
XIXb	Ethanol	118–120	$C_{25}H_{29}NO_3$	76.67	76.60	7.47	7.31
XXb	Ethanol	110–112	$C_{25}H_{29}NO_3$	76.67	76.88	7.47	7.48
XXI	Pet. ether	114–115[f]	$C_{23}H_{23}NO_2$	79.97	79.81	6.71	6.50
XXI·HCl	MeOH–but.	203–204	$C_{23}H_{23}NO_2$·HCl	72.33	72.46	6.33	6.58
XXIIa	Pet. ether	92–94	$C_{25}H_{27}NO_2$	80.39	80.11	7.29	7.08
XXIIa·CH_3I	Me_2CO–Et_2O	147–148	$C_{25}H_{27}NO_2$·CH_3I	60.58	60.32	5.87	5.84
XXIIb	95% EtOH	107–108	$C_{24}H_{25}NO_2$[e]	80.19	80.27	7.01	6.93

[a] See summary of preparations in Table I and descriptions in the experimental part. [b] Pet. ether = low boiling petroleum ether; Et_2O = diethyl ether; CH_3COOEt = ethyl acetate; but. = butanone; Me_2CO = acetone. Unless otherwise indicated all solvents are anhydrous. [c] Calcd. for OCH_3, 15.94; found, 15.76. [d] Calcd. for OC_2H_5, 21.58; found, 21.19. [e] Calcd. for OCH_3, 8.63; found, 8.22. [f] Ultraviolet absorption data were obtained by means of a Beckmann DU quartz spectrophotometer, using 95% ethanol solutions and concentrations of $5–6 \times 10^{-5}$ molar. The following data were obtained: VIIIb, λ_{max} 247 mμ (ε 12400), λ_{min} 310 mμ (ε 250); X, λ_{max} 298 mμ (ε 3100), λ_{min} 247 mμ (ε 760), 310 mμ (ε 880); IXa, λ_{max} 287 mμ (ε 4260), λ_{min} 245 mμ (ε 820), 308 mμ (ε 250); IXb, λ_{max} 290 mμ (ε 3880), λ_{min} 244 mμ (ε 760), 310 mμ (ε 540); XXI, λ_{max} 264 mμ (ε 2820), λ_{min} 232 mμ (ε 1030), 288 mμ (ε 1440). [g] Slowly oxidized at room temperature to a brown tar; pure material recovered by recrystallization from isoöctane. Stable at 0°. Prepared by general method E.

refluxed for 8 hr. with continuous stirring and neutralized with ice-cold 10% sodium hydroxide. The oily layer was extracted with ether; and the ethereal solution was dried over sodium sulfate, evaporated and distilled: yield 21.2 g. (47%), b.p. 148–150° at 11 mm.

The **hydrochloride** was prepared by dissolving a portion of the free amine in absolute ether and adding ethereal hydrogen chloride until the solution was acid to Congo red. The precipitate was crystallized from an absolute ethanol–ether mixture; m.p. 119–120°.

Anal. Calcd. for $C_{13}H_{21}NO_2$·HCl: C, 60.10; H, 8.54. Found: C, 60.21; H, 8.70.

The **hydrobromide** was prepared in the same manner and crystallized from an absolute ethanol–ether mixture; m.p. 109–110.5°.

Anal. Calcd. for $C_{13}H_{21}NO_2$·HBr: C, 51.32; H, 7.29. Found: C, 51.48; H, 7.43.

2-[N-2,2-Diethoxyethyl-N-benzylamino]-1,2-diphenylethanone VIII.—A mixture of 42.4 g. (0.19 mole) of benzylaminoacetal and 22.4 g. (0.095 mole) of desyl chloride was heated on a water-bath for three hours and allowed to cool to room temperature; ether was added. The ethereal solution was filtered to remove the benzylaminoacetal hydrochloride formed in the reaction and was then concentrated under reduced pressure. The resulting red oil was taken up in hot 95% ethanol and upon cooling gave 23.0 g. (60%) of nearly pure product which was recrystallized from 95% ethanol; m.p. 104–105°; λ_{max} 246 mμ (ε 12,700), λ_{min} 300 mμ (ε 510).

Anal. Calcd. for $C_{27}H_{31}NO_3$: C, 77.66; H, 7.48. Found: C, 77.46; H, 7.73.

Acid-catalyzed Hydrolyses, Ethanolyses and Methanolyses.—A generalized procedure was employed in these interconversions and syntheses which are listed in Table I. In a typical reaction, a mixture of 0.01 mole of the reactant and 200 ml. of 2.0 *N* hydrogen chloride in the appropriate solvent was warmed until solution was complete, and was gently refluxed for one to four hours. The solution was cooled and neutralized with a mixture of ice and 10% sodium carbonate.

The product was isolated in one of two ways as follows. (A) The free base separated upon neutralization and was collected on a filter and crystallized. (B) The neutralized solution was extracted with ether; the ether layer was dried over sodium sulfate and treated with ethereal hydrogen chloride to precipitate the hydrochloride which was then recrystallized. (C) In two preparations, the free base was prepared by basifying a small sample of the hydrochloride with 10% aqueous sodium hydroxide, extracting with ether and concentrating the ethereal solution under reduced pressure. The resulting oil was then crystallized. (D) In one preparation, the free base was isolated by extracting the basified solution with ether and concentrating the ethereal solution to an oil which was crystallized. (E) In one case the methiodide was prepared by treating an ethereal solution of the free base with methyl iodide and recrystallizing the precipitate.

Products were identified by mixture melting points with samples of previous preparations.

Unsuccessful Aluminum Isopropoxide Reductions.—A mixture of 5.0 g. (0.02 mole) of the dihydroxymorpholine X, 14.8 g. of aluminum isopropoxide and 800 ml. of dry isopropyl alcohol was slowly distilled for 20 hours; it then gave no positive test for acetone in the distillate. The excess solvent was removed under reduced pressure and the residue was treated with excess 20% sodium hydroxide and water and extracted with ether. The ethereal layer was dried over sodium sulfate and treated with ethereal hydrogen chloride to precipitate the hydrochloride. The recovery of starting material was 78%.

Employing the same procedure, the dialkoxymorpholines (IXa and b) were recovered in 92 and 90% yields, respectively.

Lithium Aluminum Hydride Reduction of 4-Benzyl-2,6-dihydroxy-2,3-diphenylmorpholine (X).—A solution of 10.0 g. (0.028 mole) of the dihydroxymorpholine in 200 ml. of absolute ether was added with continuous stirring over a period of 30 minutes to a solution of 1.06 g. of lithium aluminum hydride in 150 ml. of absolute ether. The solution was stirred for an additional hour and hydrolyzed with water and 20% sodium hydroxide, and the ether layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was crystallized from 95% ethanol; 6.4 g. (64%), m.p. 132–133°; it was identified by mixture melting point as *erythro*-1,2-diphenyl-2-benzylethanolaminoethanol (XVIII).[7a]

Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25. Found: C, 79.33; H, 7.50.

4-Benzyl-5,6-diphenyl-2-hydroxy-2,3-dihydro-1,4-oxazine (XIV).—The procedure employed is essentially that of Lutz, Freek and Murphey.[3a]

A mixture of 3.0 g. of the dihydroxymorpholine (X) and four drops of concd. hydrochloric acid was held at 120° for 15 minutes and the temperature then raised to 150° for five minutes; it was neutralized with 10% sodium carbonate

and extracted with ether. The ethereal solution was concentrated under reduced pressure and the resulting oil crystallized and was recrystallized from 95% ethanol; 0.75 g. (26%), m.p. 93–94°; λ_{max} 248 mμ (ε 11,800), 310 mμ (ε 11,300), λ_{min} 286 mμ (ε 1,540).

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.44; H, 6.16. Found: C, 80.21; H, 6.03.

This compound spontaneously decomposed slowly at room temperature and gave an oil. All attempts to prepare another solid derivative were unsuccessful.

Attempted hydrations of this compound XIV by dilute hydrochloric acid at 60° and at 80° were unsuccessful.

Lithium Aluminum Hydride Reduction of 4-Benzyl-5,6-diphenyl-2-hydroxy-2,3-dihydro-1,4-oxazine (XIV).—A solution of 5.0 g. (0.015 mole) of the hydroxydihydroöxazine XIV in 100 ml. of absolute ether was added with constant stirring over a period of 30 minutes to a solution of 0.57 g. of lithium aluminum hydride in 250 ml. of absolute ether. The mixture was stirred for an additional hour, hydrolyzed with water and 10% sodium hydroxide, and extracted with ether. The ethereal solution was concentrated under reduced pressure and the residue was poured into ice-water. The precipitate was crystallized from 95% ethanol; m.p. 102.5–104.5°. A mixture melting point with 4-benzyl-2,3-diphenyl-2-hydroxymorpholine (XXI)[7a] showed no depression.

Anal.[7a] Calcd. for $C_{25}H_{23}NO_2$: C, 79.97; H, 6.71. Found: C, 80.17; H, 6.45.

erythro-**2-(N-2,2-Diethoxyethyl-N-benzylamino)-1,2-diphenylethanol Hydrochloride (XIXa).**—A mixture of 10.0 g. (0.045 mole) of benzylaminoacetal (VII) and 5.1 g. (0.022 mole) of *trans*-stilbene chlorohydrin[17] was heated on a water-bath for four hours, cooled, and treated with absolute ether. The precipitated benzylaminoacetal hydrochloride was removed by filtration; 5.2 g. (91%). The ethereal filtrate was dried over sodium sulfate, decanted and treated with ethereal hydrogen chloride. The precipitated hydrochloride was crystallized from an absolute ethanol–ether mixture; m.p. 194–196°.

Anal. Calcd. for $C_{27}H_{33}NO_3 \cdot HCl$: C, 71.11; H, 7.52. Found: C, 70.91; H, 7.38.

The **free base** was liberated by treatment of a sample of the hydrochloride with ether and 10% aqueous sodium carbonate. The ethereal layer was concentrated and the residual pale red oil crystallized from petroleum ether; m.p. 138–139°.

Anal. Calcd. for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93. Found: C, 77.19; H, 8.01.

This compound was also prepared from the diethyl acetal VIIIa by reduction with lithium aluminum hydride and aluminum isopropoxide under the usual conditions.

threo-**2-[N-2,2-Diethoxyethyl-N-benzylamino]-1,2-diphenyl Ethanol (XXa).**—A mixture of 10.0 g. (0.045 mole) of benzylaminoacetal and 5.9 g. (0.03 mole) of *cis*-stilbene oxide[18] was heated for 12 hours at 100°. The reaction mixture was taken up in ether, dried over sodium sulfate and concentrated under reduced pressure. The residue was crystallized from ethanol; 11.0 g. (88%), m.p. 120–122°.

Anal. Calcd. for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; OC_2H_5, 21.48. Found: C, 77.44; H, 7.85; OC_2H_5, 21.01.

The **hydrochloride** was prepared by treating an ethereal solution of the free base with ethereal hydrogen chloride and recrystallization of the precipitate from an ethanol–ether mixture; m.p. 186–187°.

Anal. Calcd. for $C_{27}H_{33}NO_3 \cdot HCl$: C, 71.11; H, 7.52. Found: C, 71.28; H, 7.71.

Lithium Aluminum Hydride Reduction of 4-Benzyl-5,6-diphenyl-2-hydroxymorpholine (XXI).—A solution of 5.0 g. (0.014 mole) of the hydroxymorpholine in 100 ml. of absolute ether was added over a period of 20 minutes to a solution of 0.53 g. of lithium aluminum hydride in 200 ml. of absolute ether. The mixture was stirred for one hour and hydrolyzed with water and 20% sodium hydroxide. The ether layer was dried over sodium sulfate and concentrated; the residue was recrystallized from 95% ethanol, 3.6 g. (74%), m.p. 132–133°, and identified by mixture melting point as *erythro*-1,2-diphenyl-2-benzylethanolaminoethanol[7a] (XVIII).

α-**(N-Benzyl-N-acetalamino)-acetophenone Hydrochloride**[5] **(V).**—A solution of 10.0 g. (0.05 mole) of phenacyl bromide in 50 ml. of absolute ether was added with stirring to a solution of 10.0 g. (0.045 mole) of benzylaminoacetal (VII) and 5.0 g. (0.05 mole) of triethylamine in 50 ml. of absolute ether. After standing for 12 hours the solution was filtered to remove precipitated triethylamine hydrobromide; the ethereal filtrate was washed with dilute sodium carbonate, dried over sodium sulfate and treated with ethereal hydrogen chloride to precipitate the hydrochloride; 6.5 g. (34%); m.p. 123–124°. Recrystallization from an ethanol-ether mixture raised the melting point to 124.5–125°. The compound underwent spontaneous decomposition at room temperature and was converted to a dark oil.

Anal. Calcd. for $C_{21}H_{27}NO_3 \cdot HCl$: C, 66.73; H, 7.20. Found: C, 66.44; H, 7.37.

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Unsaturated Fatty Acids. III. Preparation of 1-C^{14}-Linoleic Acid[1]

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A method has been devised by which linoleic acid isolated from natural sources may be used as a starting material for the preparation of the substance labeled with isotopic carbon in the carboxyl group. In essence, the original carboxyl group is replaced by a bromine atom *via* the silver salt degradation of Borodin and the process reversed *via* the Grignard reaction, the sensitive and synthetically-imposing *cis,cis*-1,4-diene moiety being protected in steps where this is necessary by bromination.

Studies designed to elucidate details of the anabolism of the physiologically important arachidonic acid in mammalian tissues[2] have made the availability of C^{14}-labeled linoleic acid highly desirable, particularly in view of the wealth of deductive evidence that linoleic is an essential exogenous precursor of arachidonic acid. Several recently devised total syntheses of linoleic acid[3] have provided possible routes to such a substance, but the low over-all yields realized in these complex procedures provided incentive for a search for other approaches to the problem.

(1) This paper is based on work performed under Contract AT-04-1-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles. Certain aspects of this study were discussed before the Organic Division of the American Chemical Society in Buffalo, N. Y., March, 1952; and in an earlier Communication published in THIS JOURNAL, **74**, 1109 (1952).

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