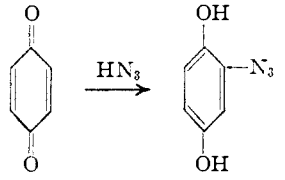
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

Addition of Hydrazoic Acid to Conjugated Systems[1]

BY J. H. BOYER

Hydrazoic acid has been added to acrolein, methyl acrylate, acrylic acid, mesityl oxide, β-nitrostyrene, acrylonitrile and α-vinylpyridine to bring about the formation of the corresponding dihydro β-azido derivatives. Cinnamic acid, its ethyl ester, cinnamaldehyde, N-methyl cinnamide and benzalacetophenone underwent no addition. It had previously been demonstrated that the acetylenic linkage, even in conjugation, reacts with hydrazoic acid to form triazoles.

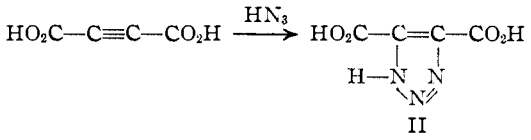
Oliveri-Mandalá in 1915 reported the formation of azidohydroquinone (I) from the addition of hydrogen azide to benzoquinone.[2] This appears



I

to be the only reported example of the formation of an azide by the addition of hydrogen azide to a conjugated system; however, azide intermediates were assumed in the formation of aminonaphthoquinones from α- and β-naphthoquinones and hydrazoic acid and quinhydrones of explosive character were obtained from toluquinone and ar-tetrahydro-α-naphthoquinone.[3]

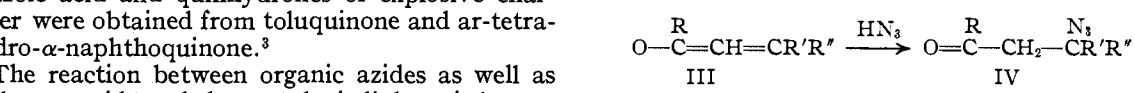
The reaction between organic azides as well as hydrogen azide and the acetylenic linkage is known to lead to triazoles. When the acetylenic linkage is part of the conjugated system in acetylene dicarboxylic acid, combination with hydrogen azide leads to triazoledicarboxylic acid (II).[4]



II

That Oliveri-Mandalá tried to realize a general reaction between the olefinic linkage and hydrogen azide as a counterpart to the reactions he had observed between acetylenic compounds and this reagent is apparent from his reaction failures with cinnamic acid, fumaric acid, styrene, vinyl bromide, ethylene and other olefinic compounds.[5,6] On the other hand, the formation of N-substituted triazolines from alkyl and aryl azides and certain olefins has been reported by several different investigators.[7-9]

It is the purpose of this paper to report additional reactions between hydrazoic acid and the conjugated olefinic linkage and to discuss certain limitations of the reaction. A study of nine α,β-unsaturated carbonyl compounds (III) revealed that variation in the nature of R has little effect on the course of the reaction, whereas a phenyl group in the "four" position (R′ = C_6H_5) appears to prevent the occurrence of the addition. Thus acrolein (IIIa), methyl acrylate (IIIb), acrylic acid (IIIc) and mesityl oxide (IIId) underwent facile addition with the formation of β-azidopropionaldehyde (IVa), methyl β-azidopropionate (IVb), β-azidopropionic acid (IVc) and 4-methyl-4-azidopentanone-2 (IVd), respectively. Cinnamic acid (IIIe), cinnamaldehyde (IIIf), ethyl cinnamate (IIIg), N-methylcinnamamide (IIIh) and benzalacetophenone (IIIi) underwent no addition. Distillation of the new azides brought about elimination of hydrogen azide (and possibly nitrogen)



III IV

	R	R′	R″		R	R′	R″
(a)	H	H	H	(f)	H	C_6H_5	H
(b)	OCH_3	H	H	(g)	OC_2H_5	C_6H_5	H
(c)	OH	H	H	(h)	$NHCH_3$	C_6H_5	H
(d)	CH_3	CH_3	CH_3	(i)	C_6H_5	C_6H_5	H
(e)	OH	C_6H_5	H				

together with regeneration of the unsaturated carbonyl compound with varying degrees of facility. β-Azidopropionaldehyde (IVa) was found to be unstable at room temperature and slowly decomposed when stored in the refrigerator; however, an anhydrous 10% chloroform solution of it was stored several weeks in the refrigerator with no decomposition. Its 2,4-dinitrophenylhydrazone was purified by recrystallization from boiling aqueous ethanol. β-Azidopropionic acid (IVc) and its methyl ester (IVb) both gave indication of decomposition upon distillation but were purified sufficiently for analysis by this method. Finally 4-azido-4-methyl-pentanone-2 (IVd) distilled with no decomposition. The same order of instability in the presence of concentrated sulfuric acid was observed; β-azidopropionaldehyde violently decomposed at room temperature, the azidoketone sluggishly evolved nitrogen at room temperature but when heated with concentrated sulfuric acid at 60° the reaction became vigorous. Traces of acid impurities were removed from ether solutions of the azides (IVa, b, d) without stripping out hydrogen azide by shaking with cold dilute aqueous sodium carbonate. In addition to their instability toward heat and concentrated sulfuric acid the azides were characterized by their infrared absorption curves (Fig. 1). Comparison with the curves reported herein for triazoacetone (Fig. 1) and β-phenylethyl azide (Fig. 2) and with the

(1) Presented at the National Meeting, A. C. S., Boston, Mass., April, 1951.

(2) E. Oliveri-Mandalá and E. Calderao, *Gazz. chim. ital.*, **45**, I, 307 (1915); E. Oliveri-Mandalá, *ibid.*, **45**, II, 120 (1915).

(3) L. F. Fieser and J. L. Hartwell, THIS JOURNAL, **57**, 1482 (1935).

(4) E. Oliveri-Mandalá and A. Coppola, *Atti accad. Lincei*, **19**, I, 563 (1910).

(5) E. Oliveri-Mandalá, *Mem. accad. Lincei*, (VI), **2**, 132 (1926).

(6) E. Oliveri-Mandalá and G. Coronna, *Gazz. chim. ital.*, **71**, 182 (1941).

(7) L. F. Fieser and J. L. Hartwell, THIS JOURNAL, **57**, 1479 (1935).

(8) L. Wolff, *Ann.*, **394**, 68 (1912); **399**, 274 (1913).

(9) K. Alder and G. Stein, *ibid.*, **485**, 211 (1931); **501**, 1 (1933).

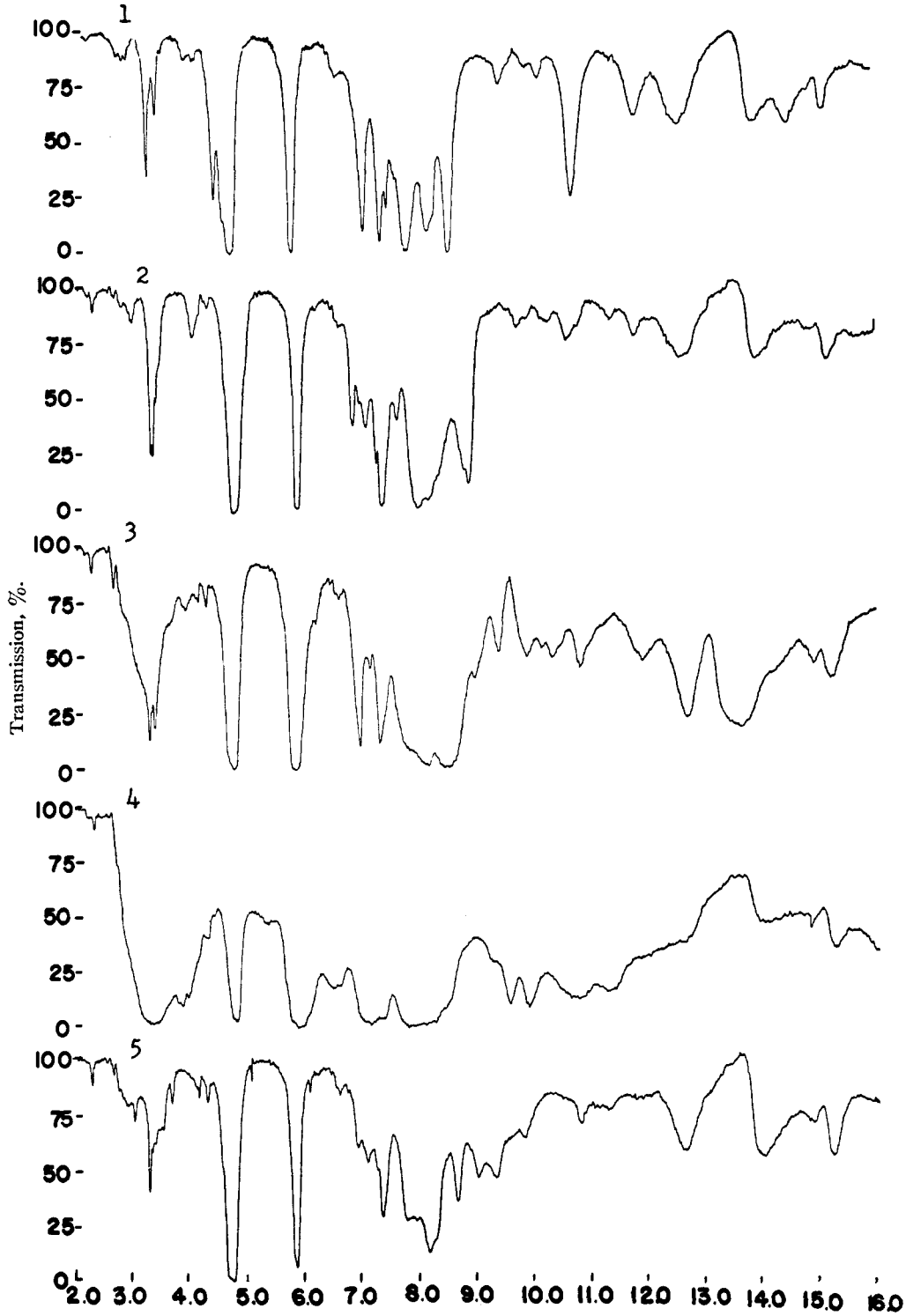


Fig. 1.—(1) Triazoacetone; (2) 4-azido-4-methylpentanone-2; (3) methyl β-azidopropionate; (4) β-azidopropionic acid; (5) β-azidopropionaldehyde.

curves previously reported for acetone,[10] methyl azide[11] and hydrogen azide[11] revealed the characteristic azide absorption band in the 4.7-μ region and a characteristic carbonyl band in the 5.9-μ region.

The ethyl esters of α- and β-azidopropionic acid had previously been prepared by the action of sodium azide on the corresponding chloro ester.[12,13] Curtius transformed each ester into the hydrazide from which he obtained well-defined crystalline

(10) D. Price, *J. Chem. Phys.*, **9**, 728 (1941).
(11) E. H. Eyster and R. H. Gillette, *ibid.*, **8**, 369 (1940).
(12) M. O. Foster and H. E. Fierz, *J. Chem. Soc.*, **93**, 669 (1908).
(13) T. Curtius and J. Franzen, *Ber.*, **45**, 1037 (1912).

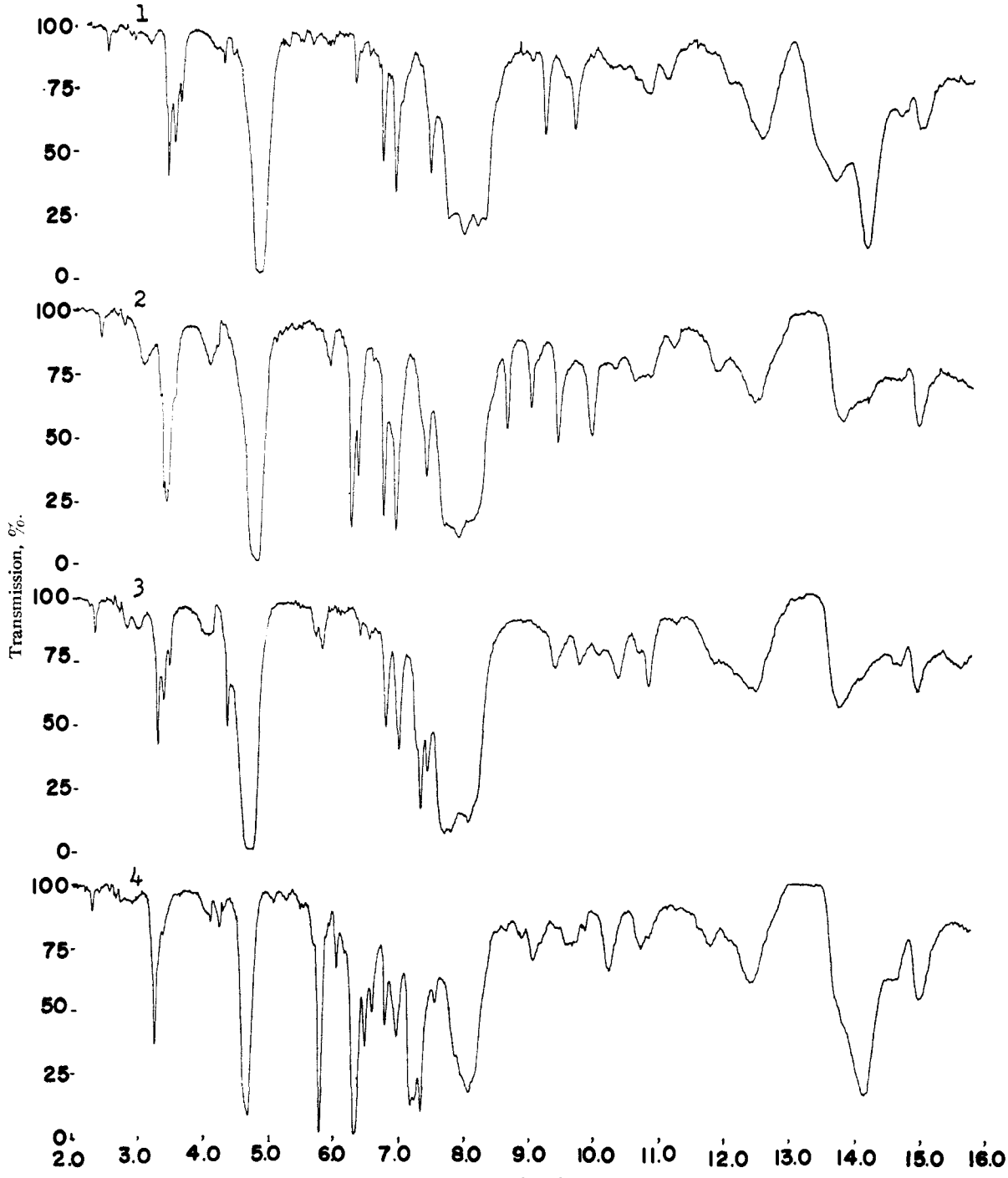


Fig. 2.—(1) β-phenylethyl azide; (2) 1-(α-pyridyl)-2-azidoethane; (3) β-azidopropionitrile; (4) 1-phenyl-1-azido-2-nitroethane.

derivatives with acetone and benzaldehyde. The action of hydrazine on methyl β-azidopropionate (IVb) brought about the formation of the hydrazide of β-azidopropionic acid identified by its benzal derivative and so established the course of the addition reaction with methyl acrylate (IVa).

The marked difference in the reactions of hydrazoic acid with olefinic and acetylenic linkages is demonstrated by comparing acrolein with propioaldehyde and acrylic acid with propiolic acid. Thus the olefinic compounds lead to azides exclusively, whereas the acetylenic compounds give only triazoles.[4,14]

Immediate reaction between β-nitrostyrene and hydrazoic acid occurred at room temperature. The product has been assigned the structure of β-nitro-α-phenyl-α-azidoethane (V) based on analogy with similar reactions reported, the strong azide absorption peak in the 4.7-μ region (Fig. 2),

(14) R. Huttel, *Ber.*, **74**, 1680 (1941).

TABLE I

Olefin	HN_3 Addition product	Yield, %	B.p., °C.	Mm.	Analyses, % Calcd.	Found	$n^{20}D^a$	$d^{20}_4{}^a$	MR_D Calcd.	Found	Decomp. by concd. H_2SO_4
CH_2=CHCHO (IIIa)	$N_3CH_2CH_2CHO^b$ (IVa)	71.0	...		Not attempted		....	....	..	..	Violent at 0°
CH_2=$CHCO_2CH_3$ (IIIb)	$N_3CH_2CH_2CO_2CH_3$ (IVb)	35.4	40–45	1	C, 37.20 H, 5.47	37.32 5.51	1.4408	1.139	30.0	29.8	Vigorous at 60°
CH_2=$CHCO_2H$ (IIIc)	$N_3CH_2CH_2CO_2H$ (IVc)	24.0	80	1	C, 31.31 H, 4.28 N, 36.51	30.90 4.15 36.76	1.4645	....	..	..	Vigorous at 60°
CH_3 | CH_3C=$CHCOCH_3$ (IIId)	CH_3 | N_3—C—CH_2COCH_3 (IVd) | CH_3	38.0	57–58	3	C, 51.04 H, 7.86 N, 29.77	51.68 7.97 29.98	1.4428	0.9955	37.7	37.6	Vigorous at 25°
C_6H_5CH=$CHNO_2$	$C_6H_5CHCH_2NO_2$[c] (V) | N_3	69.0	...		Not attempted		....	....	..	..	Violent at 0°
CH_2=$CHC{\equiv}N$	$N_3CH_2CH_2C{\equiv}N$ (VI)	17.3	64	1	C, 37.50 H, 4.20 N, 58.30	38.38 4.09 58.04	1.4570	1.1138	23.4	23.5	Vigorous at 60°
C_5H_4NCH=CH_2[d]	$C_5H_4NCH_2CH_2N_3$ (VII)	49.5	65	1	C, 56.74 H, 5.44 N, 37.82	56.61 5.35 37.39	1.5289	1.1122	41.0	41.1	Vigorous at 60°

[a] The refractive indices for methyl β-azidopropionate and 1-α-pyridyl-2-azidoethane were determined at 25°. [b] This compound decomposed upon standing at room temperature or in the refrigerator and regenerated acrolein, identified by its odor. An anhydrous 10% chloroform solution was successfully stored in the refrigerator several weeks with no decomposition. [c] Attempts to reduce this compound using stannous chloride led only to the oxime of phenylacetaldehyde, the reduction product, under these conditions, of β-nitrostyrene. [d] α-Vinylpyridine.

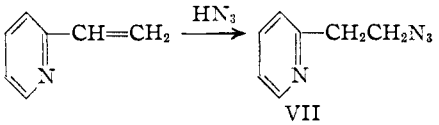
and its violent decomposition in concentrated sulfuric acid at room temperature.

$$C_6H_5CH{=}CHNO_2 \xrightarrow{HN_3} C_6H_5CH(N_3)CH_2NO_2 \quad (V)$$

Finally addition to a conjugated system containing a nitrogen atom in the "one" position was illustrated by the formation of β-azidopropionitrile (VI) and 1-α-pyridyl-2-azidoethane (VII) from acrylonitrile and α-vinylpyridine, respectively. Elementary analyses, typical azide properties (decomposition upon distillation and in the presence of concentrated sulfuric acid), conformity with the other conjugate addition products and the infrared analyses (Fig. 2) were useful in assigning azide structures to the products. It has been pointed out that conjugation of the nitrile triple bond with the carbon–carbon double bond decreases its reactivity toward addition and allows 1,4-addition to occur.[15] Accordingly no trace of vinyltetrazole which would have resulted from the addition of hydrazoic acid to the cyano group of acrylonitrile was detected. Increasing the quantity of aqueous hydrazoic and acetic acids, led to the formation of hydracrylic acid hydrate (VIII). Other 1,4-addition products of α-vinylpyridine[16] lend additional support to the structure of (VII).

$$CH_2{=}CH{-}CH{\equiv}N \xrightarrow[\text{excess acid}]{H_2O} HO{-}CH_2CH_2CO_2H{\cdot}H_2O \quad (VIII)$$

$$CH_2{=}CH{\equiv}N \xrightarrow{HN_3} N_3CH_2CH_2C{\equiv}N \quad (VI)$$



(VII)

This product was further characterized by a picrate derivative prepared in ether and recrystallized from boiling ethanol.

Experimental[17]

The Olefins.—The author is indebted to the Shell Development Company for a generous gift of acrolein and to Dr. P. A. S. Smith for ample quantities of β-nitrostyrene and N-methylcinnamamide, m.p. 110°. The acrolein (stabilized with hydroquinone) was used without further purification. β-Nitrostyrene was redistilled, b.p. 120° (1 mm.), m.p. 58°. Methylacrylate, acrylic acid, mesityl oxide, cinnamaldehyde, ethyl cinnamate, benzalacetophenone, α-vinylpyridine and acrylonitrile were commercially available and redistilled prior to use.

Preparation of the Azides.—To a solution of 0.2 mole of the olefin in 30 ml. of glacial acetic acid was added a solution of 19.5 g. (0.3 mole) of sodium azide in 75 ml. of water. The addition to acrolein (IIIa) occurred rapidly and created a highly exothermic reaction which was controlled by external cooling of the reaction mixture by an ice–salt-bath and slow addition of the sodium azide solution. β-Nitrostyrene underwent rapid addition at room temperature while methyl acrylate (IIIb), acrylic acid (IIIc) and acrylonitrile required one to three days at room temperature and mesityl oxide (IIId) and α-vinylpyridine were heated on the steam-cone for 24 hours with the hydrazoic acid solution. The remaining olefins mentioned above underwent no reaction with hydrazoic acid and were recovered unchanged after periods of refluxing with this reagent up to seven days.

The addition product in all cases was a colorless or slightly yellow oil, slightly soluble in water, from which it was readily extracted with ether. In the reaction with α-vinylpyridine the ether solution at this stage was washed with a saturated solution of sodium bisulfite to remove traces of the olefinic amine. All of the ether solutions were washed with sodium carbonate solutions with the exception of the ether solution of β-azidopropionic acid (IVc) and dried over anhydrous magnesium sulfate. Evaporation of the ether in an air-stream at room temperature left the oily azide which was purified by distillation at reduced pressure in all cases except β-azidopropionaldehyde (IVa) and β-nitro-α-phenyl-α-azidoethane (V) both of which decomposed upon heating. Physical constants, yields, and analytical data are found in Table I.

(15) C. C. Price and J. Zomlefer, *J. Org. Chem.*, **14**, 210 (1949).

(16) W. E. Doering and R. A. N. Weil, THIS JOURNAL, **69**, 246 (1947).

(17) Melting points are uncorrected. Micro analytical work was done by the Clark Semimicroanalytical Laboratory.

Careful control of reaction conditions were found to be necessary in preparing β-azidopropionitrile (VI). A solution of 5.3 g. (0.1 mole) of glacial acetic acid was treated with exactly 6.5 g. (0.1 mole) of sodium azide in 30 ml. of water and the reaction mixture stood for two to three days. In all experiments in which the concentration of hydrazoic and acetic acids was greater than that of acrylonitrile, the only product found in yields 15–20% was the monohydrate of hydracrylic acid (VIII) isolated as a colorless oil and purified by distillation, b.p. 30° (5 mm.), $n^{20}D$ 1.3749, d^{20}_4 1.0474. Strong infrared absorption at 2.7 and 5.9 μ indicated the presence of the hydroxyl and carbonyl functions, respectively.

Anal. Calcd. for $C_3H_6O_3 \cdot H_2O$: C, 33.56; H, 7.46; *MR*D, 22.8. Found: C, 33.95; H, 7.66; *MR*D, 23.5.

Triazoacetone was prepared according to the method of Forster and Fierz,[18] from chloroacetone and sodium azide. After three fractional distillations of the product a pure sample was obtained, b.p. 42–43° (2 mm.), $n^{20}D$ 1.4520.

The 2,4-dinitrophenylhydrazone derivative of β-azidopropionaldehyde (IVa) was prepared by adding five drops of the aldehyde to 8 ml. of a 1% hydrochloric acid solution of the hydrazine reagent and heating the mixture on the steam-cone for five minutes. Dilution with water brought about the separation of an orange-red solid, m.p. 115–120°. After four recrystallizations from aqueous ethanol it separated as a very fine powder, constant m.p. 129–130°.

Anal. Calcd. for $C_9H_9N_7O_4$: C, 38.71; H, 3.25; N, 35.12. Found: C, 39.50; H, 3.17; N, 35.07.

The hydrazide of β-azidopropionic acid was prepared from methyl β-azidopropionate (IVb) and hydrazine hydrate according to the directions of Curtius.[18] The **benzal derivative** was prepared by adding an equimolar quantity of benzaldehyde to the hydrazide (a thick sirup) and heating five minutes on a steam-cone. The clear solution which resulted was allowed to stand several hours in the refrigerator or until crystallization had occurred. After six recrystallizations from aqueous ethanol, the derivative separated as very fine, faintly yellow needles, m.p. 115–116° (lit.[18] m.p. 116–117°).

A picrate derivative of 1-α-pyridyl-2-azidoethane (VII) was prepared in ether. There was an immediate precipitate which was separated by filtration and recrystallized from ethanol from which it separated as yellow needles, m.p. 112–113°.

Anal. Calcd. for $C_{13}H_{11}N_7O_7$: C, 41.38; H, 2.94; N, 25.99. Found: C, 41.38; H, 2.81; N, 25.90.

Infrared Spectra.—The absorption curves given in Figs. 1 and 2 were determined with a Baird Associates double-beam infrared spectrophotometer with a sodium chloride prism, from 2% solutions in chloroform by Mr. David Brown of the Chemical Engineering Department of this University.

(18) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **93**, 81 (1908).

ANN ARBOR, MICHIGAN RECEIVED MAY 24, 1951

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A New Route to 11-Ketosteroids by Fission of a $\Delta^{9(11)}$-Ethylene Oxide[1,2]

BY HANS HEYMANN AND LOUIS F. FIESER

A previously reported product of chromic acid oxidation of methyl 3-keto-9α,11α-oxidocholanate (I) is shown to be the 3β-hydroxy-11-keto-3α,9α-oxidohemiketal (Va). This is formed *via* the 11β-hydroxy compound IVa, which can be produced by acid-catalyzed hydration of I. Similar fissions of the keto oxide I have been accomplished with hydrogen chloride and with acetic acid–boron fluoride; the hemiketals II–V have been interrelated and shown to possess highly reactive 3β-hydroxyl groups. Fission involves concerted attack of the carbonyl and oxide groups; the mechanistic formulation (a) is supported by evidence that excludes the alternate mechanism (b). The 11β-substituents in the hemiketals, shown to be β-oriented, possess unusual reactivity that is attributed to neighboring-group action of the bridging 3α,9α-oxygen atom. The 11β-hydroxy and 11-keto hemiketals IVa and Va are reducible, best by the action of sodium borohydride on the free acids, to the 3α- and 3β-acetoxy-9α,11β-dihydroxy compounds, XI and XII. These substances are convertible into the 3-epimeric 9α,11α-oxides, X and XIII; and by a series of smooth transformations, into the epimeric 3-hydroxy-11-ketocholanic acid derivatives XXII and XXIV and into the Δ^8-11-ketones XIX and XX. The triol derivative XII was proved to contain an 11β-hydroxyl group and was correlated with an 11-hydroxysteroid (XV) of the configuration attributed to cortical hormones. One surprising reaction encountered is the *cis* dehydration of triol XI to the 11-keto compound; another is Wolff–Kishner reduction of a 9α-hydroxy-11-ketone (XIV) to the $\Delta^{9(11)}$-ethylene. Of four routes found for conversion of a 3α-hydroxy-$\Delta^{9(11)}$-steroid to the 3α-hydroxy-11-ketone, three offer promise of preparative value. One involves the sequence (Chart 2): Va → XI → XIV → XVIII → XXII; others are outlined in Chart 3.

A previous paper from this Laboratory[3] reported attempts to find a way of utilizing a 9,11-unsaturated steroid as starting material for production of an 11-ketosteroid that could be used as an intermediate in the partial synthesis of cortisone. Dr. S. Rajagopalan found that the oxide resulting from the action of perbenzoic acid on methyl $\Delta^{9(11)}$-lithocholenate, now regarded as the α-oxide on the basis of evidence to be presented below, is converted by mild oxidizing agents into the 3-ketone (I), of formula $C_{25}H_{38}O_4$, and that on more drastic oxidation (CrO_3) it affords a substance $C_{25}H_{38}O_5$.

The present investigation of the new oxidation product has established that the substance is the 11-keto-3α,9α-oxidohemiketal whose structure is represented by Va. The infrared spectrum revealed the presence of hydroxyl, keto and ester functions; the free hydroxyl group, although resistant to oxidation, proved to be not only readily acylable in the presence of acids, but capable of being etherified under very mild conditions of acid catalysis reminiscent of the formation of acetals and glycosides. The substance also reacts with mercaptans, and the crystalline thioethyl derivative (Ve) on desulfuration with Raney nickel and saponification afforded the known 3α,9α-oxido-11-ketocholanic acid.[4] Confirmatory evidence of the presence of an 11-keto group was found in Clemmensen reduction of the hemiketal to 11-ketocholanic acid.[5]

On subsequent experimentation, we found that the 3-keto-9,11-oxide I can be converted into a series of related 11-substituted-3,9-oxidohemiketal derivatives. Hydrogen chloride converts I into the 11-chloro compound IIa, which readily forms a methyl ether and an acetate, and from which the keto oxide I can be regenerated. Acetolysis of I

(1) This work was supported by a grant from the Rockefeller Foundation.

(2) See Communication to the Editor, L. F. Fieser, H. Heymann and S. Rajagopalan, THIS JOURNAL, **72**, 2307 (1950).

(3) L. F. Fieser and S. Rajagopalan, *ibid.*, **73**, 118 (1951).

(4) R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

(5) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **26**, 562 (1943).