D-*threo*-acid (I) in 50 ml. of absolute ethanol was treated with dry hydrogen chloride in the same manner as previously described for the D-*erythro*-acid, but, in this case, no crystalline product formed on cooling. Evaporation of the solvent gave an oil which failed to crystallize. When this residue was treated with ethyl iminobenzoate in the manner described by Johnson and Schubert[13a] there was no evidence of a *trans*-oxazoline being formed. A thick viscous oil was obtained which appeared to be starting material.

D-*erythro*-α-Benzamido-β-benzoxy-γ-butyrolactone.—A mixture of 2.0 g. of D-*erythro*-α-amino-β-hydroxy-γ-butyrolactone hydrochloride, 17 ml. of dioxane, 2.7 g. of anhydrous potassium carbonate and 0.7 ml. of water was stirred and cooled in an ice-bath while 1.5 ml. of benzoyl chloride was added over a 15-minute period. After the addition was complete the mixture was stirred for another hour and a half and was then poured into a mixture of cracked ice and water (70 g.). The precipitate which formed was filtered off and dried on a porous plate. Recrystallization from absolute ethanol gave 0.1 g. of white needles, m.p. 177–178°. *Anal.* Calcd. for $C_{18}H_{15}NO_5$: N, 4.31. Found: N, 4.58, 4.61.

Benzoyl Migration O → N on Treatment of D-*erythro*-α-Amino-β-benzoxy-γ-butyrolactone Hydrochloride with Base.—A solution of 0.2 g. of the O-benzoyl hydrochloride (XIII) in 5 ml. of water was treated with a slight excess of dilute sodium hydroxide solution at room temperature. The solution was allowed to stand one-half hour and was then acidified to congo red paper with concentrated hydrochloric acid. After standing for several days the solid which had separated was filtered off and recrystallized from water to yield 0.14 g. (76%) of N-benzoyl acid XV, m.p. 133–136°. A mixed melting point with an authentic sample of N-benzoyl acid was not depressed.

DAVIS, CALIFORNIA

[CONTRIBUTION NO. 882 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Pyridylethylation of Active Nitrogen Compounds. II. Further Studies of the Reactions of 2-Vinylpyridine with Ketones

BY MYRON H. WILT[1] AND ROBERT LEVINE

RECEIVED OCTOBER 30, 1952

Several ketones have been pyridylethylated with 2-vinylpyridine and the structures of a number of the products have been determined. Both metallic sodium and Triton B are effective catalysts for these reactions. For the first time, the pyridylethylation of a simple ester, ethyl isobutyrate, and of a nitrile, propionitrile, are reported.

Some time ago, we reported[2] that the Michael addition of a number of ketones to 2-vinylpyridine could be effected satisfactorily in the presence of sodium metal as the condensing agent. The present report is concerned with (a) a further elucidation of the course of reaction of methyl alkyl ketones with 2-vinylpyridine, (b) the preparation of di- and tripyridylethylated ketones and (c) the establishment of satisfactory conditions for the use of benzyltrimethylammonium hydroxide (Triton B) as a pyridylethylation catalyst.

After the publication of our first report[2] in which we gave proof that in the addition of 2-vinylpyridine to methyl isobutyl ketone and methyl ethyl ketone, reaction occurred at the α-methyl carbon atom of the former ketone and at the α-methylene carbon atom of the latter ketone, a patent by Clifford[3] was brought to our attention in which it was indicated that methyl ethyl ketone is pyridylethylated at the α-methyl carbon atom. Although no proof for this claim was given by Clifford, it appeared desirable to prove the structure of the compound by a method different from that which we had used previously. Our proof of structure is shown in the following scheme. The pyridylethylated ketone, I, was converted to its semicarbazone, which was then subjected to Kishner reduction[4] to give II, which was identical with the material obtained by the alkylation of α-picoline with 1-chloro-2-methylbutane using the Chichibabin reaction as modified by Brody and Bogert.[5]

$$2\text{-}C_5H_4NCH_2CH_2CH(CH_3)COCH_3 \xrightarrow[2,\ \text{Kishner reduction}]{1,\ \text{semicarbazone}} 2\text{-}C_5H_4NCH_2CH_2CH(CH_3)CH_2CH_3$$

I II

$$2\text{-}C_5H_4NCH_3 + ClCH_2CH(CH_3)CH_2CH_3 \xrightarrow{NaNH_2} \text{II}$$

Depending on the molecular proportions of reactants (Table I), it was found that the degree of pyridylethylation of methyl ethyl ketone as well as other methyl alkyl ketones could be controlled. That the dipyridylethylated methyl ethyl ketone has both of the pyridylethyl groups on the methylene carbon atom, *i.e.*, that the compound formed was 3,3-bis-(2-(2-pyridyl)-ethyl)-2-butanone (III) was shown by the following series of reactions, involving the haloform oxidation of III to IV, which was then compared with an authentic sample. To our knowledge, the pyridylethylation of propionitrile represents the first reported use of a completely

$$(2\text{-}C_5H_4NCH_2CH_2)_2C(CH_3)COCH_3 \xrightarrow{KOCl} (2\text{-}C_5H_4NCH_2CH_2)_2C(CH_3)CO_2H$$

III IV

$$2\ 2\text{-}C_5H_4NCH{=}CH_2 + CH_3CH_2CN \xrightarrow{Na} (2\text{-}C_5H_4NCH_2CH_2)_2C(CH_3)CN$$

V

aliphatic nitrile containing no activating groups, as an addendum in a Michael reaction. Although the structure of the tripyridylethylated derivative of methyl ethyl ketone was not proved, it is probable that this compound was formed by the introduction of two pyridylethyl groups at the α-methylene car-

(1) This paper is based on part of a thesis presented by Myron H. Wilt to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(2) R. Levine and M. H. Wilt, THIS JOURNAL, **74**, 342 (1952).

(3) A. M. Clifford, U. S. Patent 2,579,419, Dec. 18, 1951.

(4) D. Todd, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, p. 396.

(5) F. Brody and M. T. Bogert, THIS JOURNAL, **65**, 1075 (1943).

bon atom and one such group at the α-methyl carbon atom of the ketone.

From the pyridylethylation of methyl isopropyl ketone, a number of products were isolated depending on the molar ratio of the reactants. The compounds isolated were the mono-(VI), di-(IX) and tripyridylethylated (X) derivatives of the ketone; dehydrated ketol, 2,5,6-trimethylhepten-4-one-3 (XI); and the compound $C_{17}H_{25}NO$ (XII), which was probably formed from the reaction of XI with 2-vinylpyridine.

That the pyridylethylation of methyl isopropyl ketone occurs first at the α-methylene carbon atom was shown by the haloform oxidation of VI to VII, which was then shown to be identical with an authentic sample obtained by the hydrolysis of VIII. The pyridylethylation of ethyl isobutyrate occurred readily in the presence of metallic sodium to give a 48% yield of VIII.[6]

$$2\text{-}C_5H_4NCH_2CH_2C(CH_3)_2COCH_3 \xrightarrow{KOCl} \underset{VI}{} \quad 2\text{-}C_5H_4NCH_2CH_2C(CH_3)_2CO_2H \ (VII)$$

$$2\text{-}C_5H_4NCH{=}CH_2 + (CH_3)_2CHCO_2C_2H_5 \xrightarrow{Na} 2\text{-}C_5H_4NCH_2CH_2C(CH_3)_2CO_2C_2H_5 \ (VIII)$$

(saponify)

While the structures of IX and X were not proved, there seems to be little doubt that in IX, the second pyridylethyl group and in X, the second and third pyridylethyl groups were introduced at the α-methyl carbon atom of VI. Although there are at least two structures for the compound $C_{17}H_{25}NO$ (XII), this material was shown to be 3,3,6,7-tetramethyl-1-(2-pyridyl)-octen-5-one-4 by the following series of reactions. The reaction of 2-vinylpyridine with XI was found also to give the compound $C_{17}H_{25}NO$, which on oxidation with 1% aqueous potassium permanganate gave VII. This oxidation establishes XII as the structure of $C_{17}H_{25}NO$ and eliminates XIII from consideration.

$$2\text{-}C_5H_4NCH_2CH_2C(CH_3)_2COCH{=}C(CH_3)CH(CH_3)_2 \ (XII)$$

$$2\text{-}C_5H_4NCH{=}CH_2 + (CH_3)_2CHCOCH{=}C(CH_3)CH(CH_3)_2 \ (XI) \xrightarrow{1\%\ KMnO_4} VII$$

$$\xrightarrow{Na} XII \text{ or } 2\text{-}C_5H_4NCH_2CH_2C(=C(CH_3)CH(CH_3)_2)COCH(CH_3)_2 \ (XIII)$$

The pyridylethylation of methyl isobutyl ketone resulted in the formation of a mixture of pyridylethylated products. It was shown earlier[2] that the monoderivative is formed by reaction of the 2-vinylpyridine at the α-methyl carbon atom of the ketone. That the dipyridylethylated ketone contains both of the pyridylethyl groups on the α-methyl carbon atom was shown by the fact that the reaction product and an authentic sample, XV, prepared as shown below, were identical.

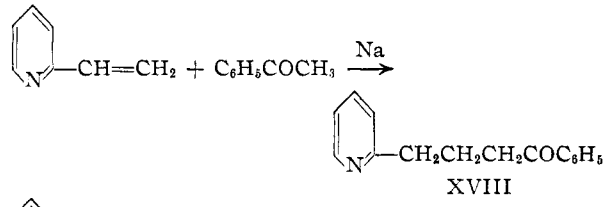
$$(CH_3)_2CHCH_2COC(H)(CO_2C_2H_5)(2\text{-}C_5H_4NCH_2CH_2) \xrightarrow[Na]{2\text{-}C_5H_4NCH{=}CH_2} (CH_3)_2CHCH_2COC(CO_2C_2H_5)(2\text{-}C_5H_4NCH_2CH_2)_2 \ (XIV)$$

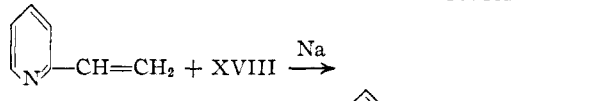
$$XIV \xrightarrow{\text{ketonic cleavage}} (CH_3)_2CHCH_2COC(H)(2\text{-}C_5H_4NCH_2CH_2)_2 \ (XV)$$

The reaction of 2-vinylpyridine with methyl *n*-amyl ketone gave a mixture of mono-(XVI) and dipyridylethylated products, while its reaction with methyl benzyl ketone gave only a monopyridylethylated derivative, XVII. That compound XVI was formed by pyridylethylation at the α-methylene carbon atom of methyl *n*-amyl ketone was established by comparison with an authentic sample, prepared from the pyridylethylation of ethyl α-*n*-butylacetoacetate and subjecting the reaction product to ketonic cleavage.

While methyl benzyl ketone has been assumed to react with 2-vinylpyridine at the α-methylene carbon atom,[7] it was desirable to prove this point. It was found that XVII, when subjected to the haloform reaction, gave 2-phenyl-4-(2-pyridyl)-butanoic acid, which was identical with an authentic sample obtained from the saponification of pyridylethylated ethyl phenylacetate.

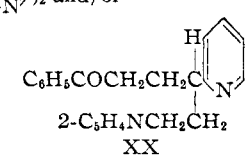
In the foregoing discussion, it has been assumed tacitly that in the dipyridylethylated ketones, the second pyridylethyl group is introduced at a carbon atom alpha to a carbonyl group. When acetophenone and propiophenone were pyridylethylated to give a mixture of mono- and di-Michael adducts, although the structures of the monopyridylethylated derivatives are unambiguous, the di-compounds could have both pyridylethyl groups attached to the α-methyl carbon atom of the starting ketone, XIX, or the second pyridylethyl group could be attached to the methylene carbon atom adjacent to the pyridine ring of the monopyridylethylated derivative, XX, as shown below with aceto-





$C_6H_5COCH(CH_2CH_2$  $)_2$ and/or

XIX



XX

(6) In this connection it is of interest to note that apparently the only other reported Michael addition in which ethyl isobutyrate was used as the addendum is the reaction of this ester with ethyl cinnamate in the presence of sodium ethoxide or sodium triphenylmethide (C. R. Hauser and B. Abramovitch, *ibid.*, **62**, 1763 (1940)) to give diethyl α,α-dimethyl-β-phenylglutarate.

(7) V. Boekelheide and J. H. Mason, THIS JOURNAL, **73**, 2356 (1951).

TABLE I

PYRIDYLETHYLATED KETONES

Ketone	Moles of reactants: Ketone	2-Vinylpyridine	Na	Triton B, g.	Reaction time, hr.	Product	Yield, %	B.p., °C.	Mm.	Formula	Nitrogen, % Calcd.	Found	Derivative	M.p., °C.	Formula	Nitrogen, % Calcd.	Found
Acetophenone	1.5	0.75		7.5	11	Mono	11.3	174–176	3	[a]							
	0.5	1.0	0.05		6	Mono	8.4										
						Di	56.8	244–247	3	$C_{22}H_{22}N_2O$	8.48	8.41	Dipicrate	173–174	$C_{34}H_{28}N_8O_{15}$	14.22	14.08
2-Acetylfuran	1.5	0.75		7.5	11	Mono	5.3	162–165	2	$C_{13}H_{13}NO_2$	6.51	6.30	Picrate	125–126	$C_{19}H_{16}N_4O_9$	12.61	12.74
Propiophenone	1.5	0.75		7.5	11	Mono	59.2	189–190	5	[a]							
	0.50	1.00	0.05		6	Mono	42.7										
						Di	45.2	263–267	4–5	$C_{23}H_{24}N_2O$	8.13	8.23	Dipicrate	73–74	$C_{35}H_{30}N_8O_{15}$	13.96	13.90
Diethyl	2.0	1.0	0.20		6	Mono	53.4	142–144	6	[a]							
						Di	31.6	238–242	6	$C_{19}H_{24}N_2O$	9.45	9.47	Dipicrate	149–150	$C_{31}H_{30}N_8O_{15}$	14.86	14.96
Diisopropyl	2.0	1.0	0.20		6	Mono	71.9	146–148	6	$C_{14}H_{21}NO$	6.39	6.50	Picrate	97–98	$C_{20}H_{24}N_4O_8$	12.50	12.63
						Di	5.3	236–238	6	$C_{21}H_{28}N_2O$	8.64	8.75	Dipicrate	148–149	$C_{33}H_{34}N_8O_{15}$	14.32	14.30
Diisobutyl	2.0	1.0	0.20		6	Mono	63.2	160–162	6	$C_{16}H_{25}NO$	5.66	5.74	Picrate	99–100	$C_{22}H_{28}N_4O_8$	11.76	11.95
						Di	14.1	242	6	$C_{23}H_{32}N_2O$	7.95	7.94	Chloroplatinate	185–187	$C_{23}H_{32}N_2O.H_2PtCl_6$	3.67	3.72
Methyl ethyl	2.0	1.0		10	11	Mono	53.3	115–117	2	[a]							
						Di	34.0	189–193	1.5–2	$C_{18}H_{22}N_2O$	9.92	9.86	Distyphnate	123–125	$C_{30}H_{28}N_8O_{17}$	14.51	14.51
	0.5	1.0	0.05		6	Mono	11.3										
						Di	31.2										
						Tri	15.5	268–270	5	$C_{25}H_{29}N_3O$	10.84	10.76	Tristyphnate	90–91	$C_{43}H_{38}N_{12}O_{25}$	14.97	14.73
Methyl isopropyl[b]	2.0	1.0	0.10		1	Mono	72.0	101–102	0.5	$C_{12}H_{17}NO$	7.32	7.32	Semicarbazone	149–150	$C_{13}H_{20}N_4O$	22.57	22.58
						Di	4.0	195–196	0.5	$C_{19}H_{24}N_2O$	9.45	9.34	Dipicrate	137–138	$C_{31}H_{30}N_8O_{15}$	14.86	14.78
						$C_{17}H_{25}NO$[c]	3.0	153–155	0.5	$C_{17}H_{25}NO$	5.40	5.66	Picrate	226–228	$C_{23}H_{28}N_4O_8$	11.47	11.28
	1.0	2.0	0.10		1	Mono	6.5										
						Di	31.0										
						Tri	39.0	282–284	5	$C_{26}H_{31}N_3O$	10.47	10.51	Tripicrate	155–157	$C_{44}H_{40}N_{12}O_{22}$	15.57	15.79
						$C_{17}H_{25}NO$[c]	6.0										
	2.0	1.0		10	11	Mono	72.2										
Methyl isobutyl	0.5	1.0	0.05		6	Mono	19.6	134–136	1.5	[a]							
						Di	34.3	208–210	1.5	$C_{20}H_{26}N_2O$	9.03	8.93	Dipicrate	162–163	$C_{32}H_{32}N_8O_{15}$	14.58	14.58
						Tri	13.4	267–269	1.5	$C_{27}H_{33}N_3O$	10.12	10.21	Tristyphnate	89–90	$C_{45}H_{42}N_{12}O_{25}$	14.74	14.81
Methyl *n*-amyl	1.0	0.5	0.10		6	Mono	38.6	155–156	3–4	$C_{14}H_{21}NO$	6.39	6.56	Semicarbazone	155–156	$C_{15}H_{24}N_4O$	20.27	20.28
						Di	18.7	210–214	1	$C_{21}H_{28}N_2O$	8.64	8.60	Dipicrate	91–92	$C_{33}H_{34}N_8O_{15}$	14.32	13.98
	1.5	0.75		7.5	11	Mono	3.2										
Methyl benzyl	1.0	0.5	0.1		6	Mono	44.3	162–164	2				Picrate[d]	67–68	$C_{22}H_{20}N_4O_8$	11.96	11.99

[a] See ref. 2. [b] In the reaction with this ketone, considerable amounts of 2,5,6-trimethylhepten-4-one-3, b.p. 189–191° (746 mm.), and 102–104° (45 mm.) (W. Wayne and H. Adkins, THIS JOURNAL, **62**, 3402 (1940)) were obtained; 2,4-dinitrophenylhydrazone, m.p. 84–85° (H. J. Shine and E. E. Turner, *J. Inst. Petroleum*, **36**, 73 (1950)). [c] This compound is 3,3,6,7-tetramethyl-1-(2-pyridyl)-octen-5-one-4 (see Experimental). [d] Boekelheide and Mason (see ref. 7) report the m.p. of this picrate to be 131–132°.

phenone. Although it is unlikely that the dipyridylethylated compound has structure XX, this structure cannot be disregarded *a priori* since Leonard and Boyer[8] have shown that 2-picoline undergoes Michael addition to 2-vinylpyridine in the presence of sodium. Therefore, an attempt was made to pyridylethylate 2-*n*-amylpyridine (whose α-methylene carbon atom carries hydrogen atoms of about the same reactivity as those adjacent to the pyridine ring in monopyridylethylated acetophenone) using conditions which led to a good yield of dipyridylethylated acetophenone. However, no reaction occurred. This result appears to indicate that dipyridylethylated acetophenone has structure XIX not XX. Furthermore, ethyl benzoylacetate was dipyridylethylated and when the resulting product was subjected to ketonic cleavage, a compound identical with that obtained in the dipyridylethylation of acetophenone was isolated.

It may be seen (Table I) that Triton B was an effective catalyst for the pyridylethylation of several ketones. Because of the thermal instability of this catalyst, a lower temperature (70–75°) and longer reaction times were required to give yields comparable to those obtained with a metallic sodium catalyst. Furthermore, using Triton B, somewhat higher yields were obtained if the catalyst was added portionwise during the course of the reaction rather than all at once at the start of the reaction.

Experimental

I. Pyridylethylation of Ketones. (a) Using Sodium as the Catalyst.—A mixture of either two moles of ketone and one mole of 2-vinylpyridine or one mole of ketone and two moles of 2-vinylpyridine, depending on whether it was desired to prepare the mono- or dipyridylethylated derivative as the major reaction product, was placed in the previously described apparatus.[2] To the rapidly stirred mixture 0.1–0.2 mole of small cubes of sodium was added all at once. After a few minutes of stirring, a highly exothermic reaction started. The reaction temperature was kept between 70–75° by the intermittent use of a cooling bath and when the exothermic reaction subsided, the mixture was refluxed for the appropriate length of time (see Table I), cooled to room temperature and worked up as described previously.[2]

(b) Using Triton B as the Catalyst.—The apparatus employed was the same as that employed in part (a) above except for the absence of a drying tube in the reflux condenser. The proportions of reactants listed in Table I and 5 g. of Triton B were placed in the flask and the rapidly stirred mixture was heated to 70–75° for the appropriate length of time. During this period 1-g. quantities of Triton B were added hourly until all the catalyst had been added. The mixture was then worked up in the regular fashion.[2]

II. The Structure of Monopyridylethylated Methyl Ethyl Ketone (I). (a) The Kishner Reduction of the Semicarbazone of I.—A mixture of 14.0 g. (0.06 mole) of the semicarbazone of I (m.p. 153–154°) and 7.0 g. (0.13 mole) of powdered potassium hydroxide was heated in a small distilling flask; and from the molten mixture, gas was evolved and 8.0 g. of an oil, b.p. 215–230°, distilled and was condensed. Redistillation gave 5.0 g. (51%) of 2-(3-methylamyl)-pyridine (II) b.p. 134–136° (50 mm.). *Anal.* Calcd. for $C_{11}H_{17}N$: N, 8.58. Found: N, 8.57. Chloroplatinate, yellow-orange crystals, m.p. 175–176°. *Anal.* Calcd. for $2C_{11}H_{17}N \cdot H_2PtCl_6$: N, 3.80. Found: N, 3.76.

(b) 2-(3-Methylamyl)-pyridine (II).—The sodium amide from 11.5 g. (0.5 mole) of sodium, 23.4 g. (0.25 mole) of 2-picoline and 26.7 g. of 1-chloro-2-methylbutane were refluxed for 16 hours using the procedure of Brody and Bogert[5] and gave 13.3 g. of 2-(3-methylamyl)-pyridine, b.p. 121–133° (48 mm.). This material gave a yellow-orange chloroplatinate, m.p. 175–176° alone and when mixed with the material prepared in II (a).

III. The Structure of Dipyridylethylated Methyl Ethyl Ketone (III). (a) Oxidation of III with Potassium Hypochlorite.—To a solution of potassium hypochlorite prepared from 11 g. of calcium hypochlorite ("HTH") was added 5.6 g. (0.02 mole) of III and the mixture stirred overnight at room temperature. The excess hypochlorite was destroyed by the addition of sodium bisulfite solution and a small amount of unreacted III was removed by extraction with benzene. After acidification with glacial acetic acid to a *p*H of five, the solution was extracted with three 100-ml. portions of benzene and the combined extracts were dried by refluxing under a Dean–Stark tube. The cooled solution was then saturated with dry hydrogen chloride to give 2.9 g. (41%) of the dihydrochloride of 2,2-bis-(2-(2-pyridyl)-ethyl)-propanoic acid, m.p. 210–212° (from absolute ethanol). *Anal.* Calcd. for $C_{17}H_{20}N_2O_2 \cdot 2HCl$: N, 7.84; Cl, 19.85. Found: N, 7.79; Cl, 19.68.

(b) 2,2-Bis-(2-(2-pyridyl)-ethyl)-propanenitrile (V).—A mixture of 55.1 g. (1.0 mole) of propionitrile, 210.4 g. (2.0 moles) of 2-vinylpyridine and 2.3 g. (0.1 mole) of sodium was refluxed for six hours. On working up the reaction mixture in the regular way, 30.0 g. (19.3%) of 2-(2-(2-pyridyl)-ethyl)-propanenitrile, b.p. 115–117° (4 mm.), was obtained. *Anal.* Calcd. for $C_{10}H_{12}N_2$: N, 17.49. Found: N, 17.40. This compound formed a yellow crystalline picrate, m.p. 117–118°. *Anal.* Calcd. for $C_{16}H_{15}N_5O_7$: N, 18.00. Found: N, 18.32. There was also obtained 104.2 g. (39.4%) of V, b.p 208–210° (4 mm.). *Anal.* Calcd. for $C_{19}H_{19}N_3$: N, 15.83. Found: N, 15.70. This material gave a yellow crystalline dipicrate, m.p. 173–174°. *Anal.* Calcd. for $C_{29}H_{25}N_9O_{14}$: N, 17.43. Found: N, 17.61.

(c) 2,2-Bis-(2-(2-pyridyl)-ethyl)-propanoic Acid (IV).—To 100 ml. of 75% sulfuric acid containing 2 g. of sodium chloride, was added 10.6 g. (0.04 mole) of V and the resulting solution heated at 160° for 30 minutes and then at 175° for 45 minutes. The mixture was cooled to room temperature, poured onto 200 g. of ice, made alkaline with 30% sodium hydroxide solution and extracted several times with benzene. The combined extracts were then acidified to a *p*H of five with glacial acetic acid, the acidified extracts re-extracted with benzene, the benzene extracts dried (Dean–Stark tube) and the dried extracts saturated with anhydrous hydrogen chloride to give 8.3 g. (58%) of the dihydrochloride of IV, which was recrystallized from absolute ethanol and melted at 210–212° alone and when mixed with a sample of the material described in III(a) above.

IV. The Structure of Monopyridylethylated Methyl Isopropyl Ketone (VI). (a) Oxidation of VI with Potassium Hypochlorite.—The potassium hypochlorite solution prepared from 55.0 g. of HTH was added slowly with vigorous stirring to a mixture of 21.0 g. (0.11 mole) of VI, 10.0 g. of sodium hydroxide and 50 ml. of water. A vigorous reaction occurred and the reaction temperature was maintained at 60° by the use of an ice-bath when necessary. The clear solution, which was present after 45 minutes, was cooled and treated with 40% sodium bisulfite solution to destroy the excess hypochlorite. The acidification of the solution with glacial acetic acid caused the precipitation of a voluminous white solid, which was filtered, washed with water and dried and consisted of 16.5 g. (78%) of 2,2-dimethyl-4-(2-pyridyl)-butanoic acid (VII), m.p. 162–163° (from aqueous ethanol). *Anal.* Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.20.

(b) 2,2-Dimethyl-4-(2-pyridyl)-butanoic Acid (VII).—A mixture of 86.0 g. (0.75 mole) of ethyl isobutyrate, 79.0 g. (0.75 mole) of 2-vinylpyridine and 1.7 g. (0.08 mole) of sodium was refluxed for six hours and worked up in the regular way to give 79.7 g. (48.3%) of ethyl 2,2-dimethyl-4-(2-pyridyl)-butanoate, b.p. 127–129° (2 mm.). *Anal.* Calcd. for $C_{13}H_{19}NO_2$: N, 6.33. Found: N, 6.36. This ester formed a yellow crystalline picrate, m.p. 87–88°. *Anal.* Calcd. for $C_{19}H_{22}N_4O_9$: N, 12.44. Found: N, 12.50. A mixture of 10.0 g. (0.05 mole) of this ester, 10.0 g. of sodium hydroxide and 100 ml. of water was refluxed until all the oil present had dissolved. On cooling and acidifying the reaction mixture with glacial acetic acid, 7.8 g. (40.4%) of VII was obtained, which when recrystallized from aqueous ethanol gave white crystals, m.p. 162–163° alone and when mixed with a sample of the material described in IV(a).

V. The Structure of Compound $C_{17}H_{25}NO$: 3,3,6,7-Tetramethyl-1-(2-pyridyl)-octen-5-one-4 (XII). (a) Oxidation of

(8) N. J. Leonard and J. H. Boyer, THIS JOURNAL, **72**, 4818 (1950).

XII with Potassium Permanganate.—To three liters of dilute potassium permanganate solution (30 g. of $KMnO_4$ in 3000 ml. of water) was added 10.0 g. (0.04 mole) of XII, and the mixture stirred for 16 hours at room temperature. The manganese dioxide, which had formed, was filtered, the filtrate evaporated to about 300 ml., acidified with glacial acetic acid and then evaporated to dryness. The resulting solid was pulverized, extracted several times with boiling absolute ethanol and the ethanol distilled. A viscous oil remained and this material crystallized after standing for several weeks to give 3.5 g. of VII, m.p. 162–163° (from aqueous ethanol) alone and when mixed with a sample of the material described in IV (a).

(b) **The Reaction of 2-Vinylpyridine with 2,5,6-Trimethylhepten-4-one-3 (XI).**—A mixture of 8.5 g. (0.05 mole) of XI, 5.2 g. (0.05 mole) of 2-vinylpyridine and 0.2 g. (0.01 mole) of sodium was refluxed for six hours and worked up in the regular way to give 4.0 g. (29.1%) of XII, b.p. 170° (4 mm.) and 153–155° (0.5 mm.). The picrate of this material melted at 226–228° alone and when mixed with the same compound obtained as a by-product in the pyridylethylation of methyl isopropyl ketone.

VI. The Structure of Monopyridylethylated Methyl *n*-Amyl Ketone (XVI).—A mixture of 110.0 g. (0.60 mole) of ethyl α-*n*-butylacetoacetate, 63.0 g. (0.60 mole) of 2-vinylpyridine and 1 g. (0.04 mole) of sodium was refluxed for 12 hours and worked up to give some pyridylethylated material and 106 g. of unreacted β-ketoester. This material was dried and treated with more 2-vinylpyridine and sodium. The bases isolated from both runs were combined and distilled to give 11.5 g. (3.4%) of ethyl α-*n*-butyl-α-(β-(2-pyridyl)-ethyl)-acetoacetate, b.p. 145–185° (4 mm.). This material was dissolved in a mixture of 30 ml. of concentrated hydrochloric acid and 30 ml. of water and refluxed for 10 hours to give, after being worked up in the customary manner, 5.0 g. (55.5%) of 3-*n*-butyl-5-(2-pyridyl)-2-pentanone, b.p. 150–156° (4 mm.); semicarbazone, m.p. 155–156° alone and when mixed with a sample obtained from the direct monopyridylethylation of methyl *n*-amyl ketone.

VII. The Structure of Monopyridylethylated Methyl Benzyl Ketone (XVII).—On oxidizing 4.0 g. (0.02 mole) of XVII with potassium hypochlorite in the customary fashion 1.1 g. (27.3%) of 2-phenyl-4-(2-pyridyl)-butanoic acid, m.p. 159–160°, was obtained. *Anal.* Calcd. for $C_{15}H_{15}NO_2$: N, 5.81. Found: N, 5.81. A mixed melting point of this acid with that obtained from the saponification of monopyridylethylated ethyl phenylacetate[9] showed no depression.

(9) H. Reich and R. Levine, unpublished observations from this Laboratory.

PITTSBURGH, PENNSYLVANIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Mycomycin. III. The Structure of Mycomycin, an Antibiotic Containing Allene, Diacetylene and *cis*, *trans*-Diene Groupings[1]

BY WALTER D. CELMER AND I. A. SOLOMONS

RECEIVED SEPTEMBER 18, 1952

The antibiotic mycomycin, $C_{13}H_{10}O_2$, is an optically active, eightfold unsaturated, carboxylic acid which yields *n*-tridecanoic acid upon catalytic hydrogenation. Chemical and spectral data disclose allene, diacetylene and conjugated diene groupings in mycomycin and lead to its formulation as (−)-3,5,7,8-*n*-tridecatetraene-10,12-diynoic acid (Ia). The 3,5-diene in mycomycin is further characterized as possessing a *trans,cis* stereoconfiguration. Mycomycin undergoes a unique rearrangement in aqueous alkali, involving an allene to acetylene conversion, a dual acetylenic migration and a *trans,cis* to *trans,trans* isomerization, yielding optically inactive isomycomycin, 3(*trans*),5(*trans*)-*n*-tridecadiene-7,9,11-triynoic acid (IIa). Mycomycin represents the first reported example of an optically active allene of natural origin.

Mycomycin,[2a] $C_{13}H_{10}O_2$, is an optically active, $[\alpha]^{25}D$ −130°, highly unsaturated carboxylic acid, shown to be (−)-3,5,7,8-*n*-tridecatetraene-10,12-diynoic acid (Ia).[2b] This antibiotic is inherently

$$HC{\equiv}C{-}C{\equiv}CCH{=}C{=}CHCH{=}CHCH{=}CHCH_2CO_2R$$
Ia, R = H; Ib, R = CH_3

unstable. The crystalline compound rapidly darkens at room temperature (losing one-half of its antibiotic activity in three hours) and explodes at its melting point, 75°.

In the presence of dilute aqueous alkali, mycomycin is rapidly converted to an isomeric acid, isomycomycin, which has the structure 3,5-*n*-tridecadiene-7,9,11-triynoic acid (IIa).[3]

$$CH_3C{\equiv}CC{\equiv}C{-}C{\equiv}CCH{=}CHCH{=}CHCH_2CO_2R$$
IIa, R = H; IIb, R = CH_3

It is the purpose of this paper to discuss in detail the chemical and spectral properties of mycomycin which led to a previous abbreviated announcement[2b] of its structure. Herein, mycomycin and isomycomycin are further characterized in regard to the stereoconfiguration of their 3,5-diene structural units. It is shown that mycomycin undergoes in addition to an allene to acetylene conversion and a dual acetylenic migration,[3] a *trans,cis* to *trans,trans* isomerization during its alkaline-induced rearrangement to isomycomycin.

Unbranched Chain.—Early characterization work on mycomycin revealed that complete catalytic hydrogenation required eight moles of hydrogen and gave a quantitative yield of *n*-tridecanoic acid.[2] The linear nature of this reduction product eliminates the possibility of branching and/or ring structure and establishes the chain length in the original mycomycin molecule.

—C≡CH.—The presence of a monosubstituted acetylene is indicated by the reactivity of both mycomycin and its methyl ester with acetylenic hydrogen reagents such as alcoholic silver nitrate.[4] This grouping is further substantiated by intense, well-defined, infrared absorption exhibited by the ester near 3280 cm.$^{-1}$ (Fig. 1) which is the characteristic hydrogen stretching frequency associated

(1) Presented before the Division of Medicinal Chemistry at the Atlantic City Meeting of the American Chemical Society, September 17, 1952. Abstracts of Papers, p. 17L.

(2) (a) W. D. Celmer and I. A. Solomons, THIS JOURNAL, **74**, 2245 (1952); (b) W. D. Celmer and I. A. Solomons, *ibid.*, **74**, 1870 (1952).

(3) W. D. Celmer and I. A. Solomons, Abstracts 121st American Chemical Society Meeting, Milwaukee, Wis., April, 1952, p. 93K; THIS JOURNAL, **74**, 3838 (1952).

(4) A. Behal, *Ann. chim.*, **15**, 408 (1888).