STUDY OF SYNTHETIC ROUTES TO VITAMINS B_1 AND B_6, DIHYDROSPHINGOSINE, TRYPTAMINE, AND URIDINE BASED ON THE DAKIN – WEST REACTION *

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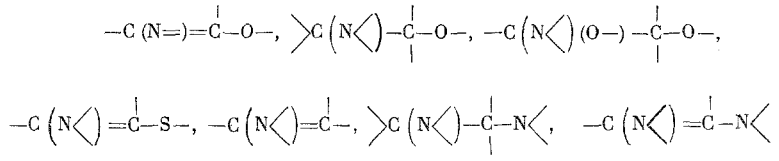
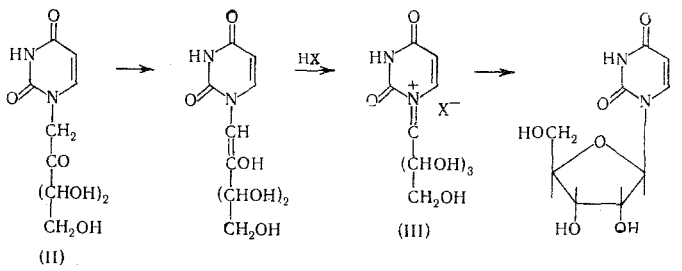
The first stages of biosynthesis of natural compounds so varied in their structure and functions as are biotin [1] and porphyrin [2] are accomplished by one and the same method, that of C-acylation of α-amino acids to α-amino ketones, known in organic chemistry under the name Dakin–West reaction [3]. A similar biogenetic universality is also characteristic of other biochemical reactions, for example for the transamination and C-hydroxymethylation participating in the biosynthesis of various amino acids, pyrimidines, and purines [2]. In consequence it is logical to assume that the biochemical role of the Dakin–West reaction is not limited to the cases mentioned above and extends to the biosynthesis of certain other natural compounds with two carbon fragments of the type



which can be synthesized starting from an α-amino ketone grouping.

Thus, starting from α-alanine, glycine, N-phenylglycine, serine, and uracil-1-acetic acid (I) it is easy to represent, for example, the formation of vitamins B_1 and B_6, ephedrine, amino sugars, pilocarpine, auxin, tryptamine, sphingolipids, chloramphenicol, and nucleosides (Table 1). The transformations used in these schemes do not require special comment since they have more or less close biochemical and chemical analogies. It should only be noted that the prerequisite for the cyclization of (II) to uridine (see Table 1, example 12) is the presence of electrophilic properties on C_1 of the sugar residue, the quaternary ammonium salt (III), for example, may possess these



(II) (III)

In order to study the above amino ketone principle of synthesis of molecules of natural compounds we have

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TABLE 1

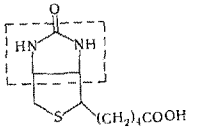
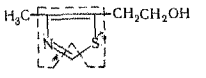
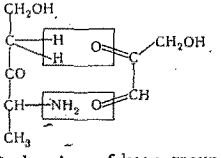
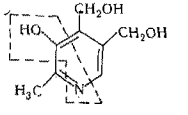
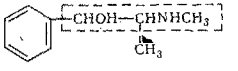
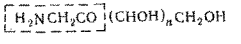
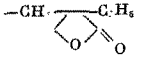
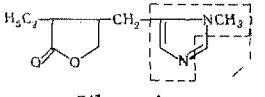
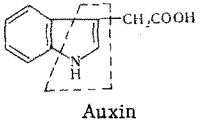
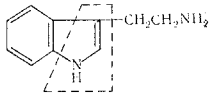
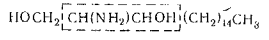
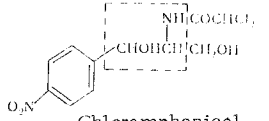
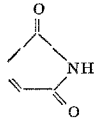
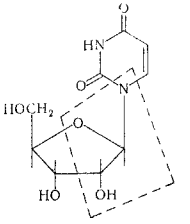
Expt., No.	Precursors participating in the Dakin–West reaction: RCH (NR_1R_2)COOH R	R_1	R_2	R_3COOH R_3	Conversions of products of the Dakin–West reaction $RCH(NR_1R_2)COR_3$	Biochemical analogies of these conversions	Conversion products of $RCH(NR_1R_2)COR_3$
1	CH_3	H	H	$(CH_2)_3COOH$	Carbamidation, reduction, and sulfur incorporation [1]	—	 Biotin
2	H	H	H	$(CH_2)_2COOH$	Self condensation [2]	—	Porphyrin
3	CH_3	H	H	$(CH_2)_2OH$	N-Formylation and sulfur incorporation	N-Formylation of glycine amide ribonucleotide [2], sulfur incorporation into alcohols and aldehydes [2, 4]	 Thiazole portion of vitamin B_1
4	CH_3	H	H	$(CH_2)_2OH$		Formation of piperidine ring from amino aldehyde [2]	 Vitamin B_6
5	CH_3	H	H	C_6H_5	Reduction of keto group and N-methylation	Reduction of aliphatic ketones to alcohols, N-methylation of tyramine [2]	 Ephedrine
6	H	H	H	$(CHOH)_nCH_2OH$	—	—	 Amino sugars
7	H	H	H		Reaction with CH_2O and NH_3, N-methylation	Formation of piperidine ring from amino aldehyde [4], N-methylation of tyrmine [2]	 Pilocarpine
8	H	H	C_6H_5	CH_2COOH	Cyclization	Formation of indole-3-glycerophosphate from 1-deoxyribonucleotide anthranilic acid [2]	 Auxin

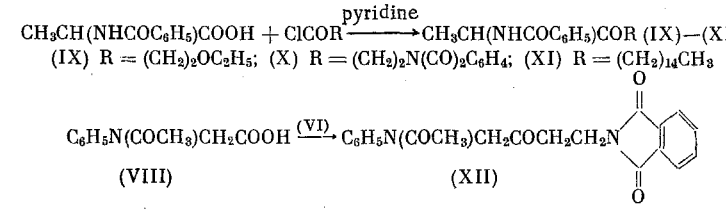
TABLE 1 (Continued)

Expt. No.	Precursors participating in the Dakin–West reaction				Conversions of products of the Dakin–West reaction $RCH(NR_1R_2)COR_3$	Biochemical analogies of these conversions	Conversion products of $RCH(NR_1R_2)COR_3$
	$RCH(NR_1R_2)COOH$			R_3COOH			
	R	R_1	R_2	R_3			
9	H	H	C_6H_5	$(CH_2)_2NH_2$	»	The same	 Tryptamine
10	CH_2OH	H	H	$(CH_2)_{14}CH_3$	Reduction of keto group	Reduction of aliphatic ketones [4]	 Dihydrosphigosine
11	CH_2OH	H	$COCHCl_2$	$C_6H_4NO_2$ *p*	The same	The same	 Chloramphenicol
12	H			$(CHOH)_2CH_2OH$	Cyclization	q. v. Text of paper	 Uridine

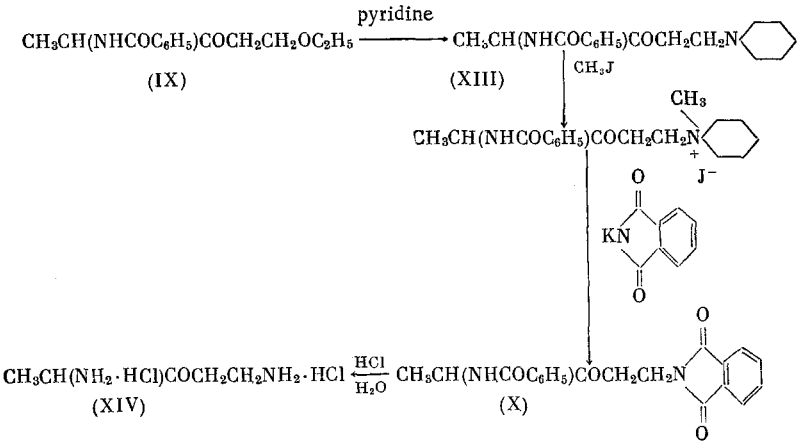
Note: the two carbon fragments formed from the amino keto grouping are enclosed by the dotted lines.

investigated under chemical conditions the Dakin–West reaction with N-acyl derivatives of the α-amino acids which enter into the hypothetical schemes of biosynthesis of vitamins B_1 and B_6, dihydrosphingosine, tryptamine, and uridine (see Table 1, examples 3, 4, 9, 10, and 12).

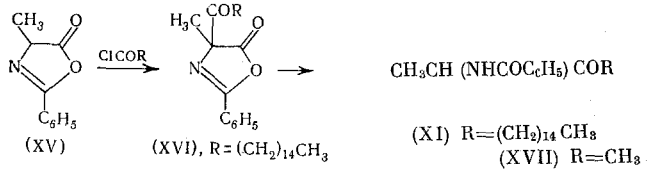
On reacting α-N-benzoylalanine (IV) with the acid chlorides of β-ethoxypropionic (V), β-phthalimidopropionic (VI), and palmitic acid (VII) and also N-phenyl-N-acetylglycine (VIII) with (VI) according to a novel variation of the Dakin–West reaction [5] the corresponding α-amino ketones (IX)-(XII) were obtained in 40-70% yield. These ketones contain in their composition the structural elements required for the subsequent conversion into the thiazole portion of vitamin B_1, vitamin B_6, deoxydihydrosphingosine, and tryptamine in accordance with schemes given in Table 1 (examples 3, 4, 9, and 10)



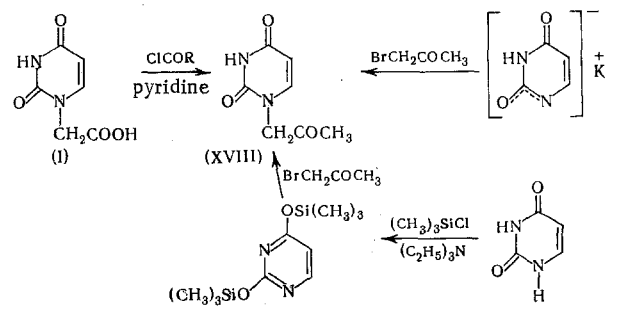
The structure of (IX) and (X) was confirmed by the conversion of (IX) into (X) via the intermediate methiodide (XIII) and also by the hydrolysis of (X) to the diamino ketone dihydrochloride (XIV)



Compound (XI) was also prepared by heating 2-phenyl-4-methyloxazolin-2-one (XV) with (VII) in pyridine and subsequent cleavage of the intermediate C-acyl derivative (XVI) (yield ~70%). The previously recorded low yield of α-amino ketone (XVII) from the reaction of (XV) with CH_3COCl is apparently explained by the instability of this acid chloride in pyridine medium [5]



The main opportunity to introduce uracil-1-acetic acid (I) to the Dakin–West reaction is shown in the simplest C-acetylation example. The 1-acetonyluracil (XVIII) formed in this is identical to the alkylation products of the K-salt and the bistrimethylsilyl derivative of uracil with bromoacetone



The structure of (IX)-(XII) was confirmed by the IR spectra which contained ketone and amide group frequencies in the 1640-1800 cm^{-1} region (see "Experimental" section).

EXPERIMENTAL

α-N-Benzoylaminoethyl-β-ethoxyethyl Ketone (IX). To a solution of 0.2 g of D, L-α-N-benzoylalanine (IV) in 2 ml of anhydrous pyridine was gradually added 0.47 g of the acid chloride β-ethoxypropionic acid (V) [6]. The reaction mixture was heated for 1 h at 90-100°C then the pyridine was distilled off in vacuum, the residue was treated with water, and extracted with benzene. The benzene extract was washed with $NaHCO_3$ solution and dried over $MgSO_4$. After removal of the solvent the residue was crystallized at – 60°C from a mixture of ether and hexane. This gave 0.1 g (39%) of (IX) with mp 48-49°C. The R_f (here and subsequently thin-layer chromatography (TLC) on Al_2O_3 activity III, detection of spots with iodine vapor and in UV light) was 0.51 (benzene–ethyl acetate, 2:1). IR spectrum $(CHCl)_3$; 1725, 1650 cm^{-1}. Found° N 5.64; 5.66%. $C_{14}H_{19} \cdot NO_3$. Calculated: N 5.62%.

n-Pentadecyl-α-N-benzoylaminoethyl Ketone (XI). A mixture of 0.5 g of (IV) and 1.5 g of palmitoyl chloride (VII) in 10 ml of pyridine was heated for 1.5 h at 100° then evaporated under vacuum, the residue was treated with benzene and applied to a column of Al_2O_3 activity III. Benzene and a mixture of benzene and ethyl acetate, 1:1, eluted 0.66 g (68%) of n-pentadecyl-α-N-benzoylaminoethyl ketone (XI) with mp 80-82°C, R_f 0.85 (benzene–ethyl acetate). IR spectrum (KBr): 1720, 1640 cm^{-1}. Found: C 77.77; 77.56; H 10.75; 10.58; N 3.95; 3.63%. $C_{25}H_{41}NO_2$. Calculated: C 77.50; H 10.58; N 3.62%.

A mixture of 0.4 g of 2-phenyl-4-methyloxazolin-2-one (XV) [7] and 0.65 g of (VII) in 5 ml of pyridine was heated for 1.5 h at 100°C then evaporated in vacuum, the residue was mixed with 5 ml of CH_3COOH and 5 ml of dilute HCl (1:1), the mixture was heated for 20 min at 70-80°C and evaporated anew. After the above treatment 0.65 g (73%) of (XI) was obtained with mp 82-84°C.

α-N-Benzoylaminoethyl-β-piperidinoethyl Ketone (XIII). A mixture of 1.93 g of (IX), 1 ml of water, and 10 ml of piperidine was heated for 4 h and then evaporated to dryness in vacuum, dilute HCl (1:4) was added to the residue until the pH was 4, the mixture was filtered, the filtrate was basified with K_2CO_3 and extracted with benzene. From the benzene extract 1.5 g (67%) of (XIII) was isolated as an oil with R_f 0.24 (benzene–ethyl acetate, 1:1). On passing gaseous HCl into an ethereal solution of (XIII) the hydrochloride was precipitated and had mp 173-175°C. Found: C 62.39; 62.67; H 7.30; 7.53; Cl 10.74; 10.78; N 8.71%. $C_{17}H_{25}ClN_2O_2$. Calculated: C 62.80; H 7.70; Cl 10.92; N 8.63%. On maintaining (XIII) with excess CH_3I in acetone (~24 h, ~20°) the methiodide was formed and had mp 318-320°C. Found: N 6.21; 6.26%. $C_{18}H_{27}I \cdot N_2O_2$. Calculated: N 6.52%.

α-N-Benzoylaminoethyl-β-phthalimidoethyl Ketone (X). A mixture of 0.56 g of (IV) and 1.5 g of β-phthalimidopropionoyl chloride (VI) [8] in 8 ml of anhydrous pyridine was heated for 5 h at 100-105°C. The pyridine was distilled off in vacuum, the residue was extracted with benzene, the benzene extract was washed with water, $NaHCO_3$ solution, and dried over $MgSO_4$. After removal of the solvent the residue was recrystallized from the minimum quantity of benzene. This gave 0.31 g of (X) with mp 152-154°C. A further 0.69 g of (X) with mp 149-153°C was precipitated from the mother liquor by the addition of ether, the overall yield was 68% of theory. The R_f was 0.40 (benzene–ethyl acetate, 1:2). IR spectrum $(CHCl_3)$: 1780, 1720, 1665 cm^{-1}. Found: C 68.27; 68.52; H 5.12; 5.11; N 8.17; 8.02%. $C_{20}H_{18}N_2O_4$. Calculated: C 68.57; H 5.14; N 8.00%. A mixture of 0.2 g of methiodide (XIII) and an equivalent quantity of potassium phthalimide in 10 ml of alcohol was boiled for 4 h, the mixture was evaporated to dryness in vacuum, the residue was treated with water, (X) was extracted with benzene and had mp 152-154°C, it did not give a melting point depression in mixture with the sample described above.

A mixture of 0.6 g of (X) and 20 ml of concentrated HCl was boiled for 14 h then evaporated to dryness in vacuum, the residual water and HCl were removed by distillation with benzene. The benzoic and phthalic acid which were formed were extracted with anhydrous acetone. The residue was recrystallized from a mixture of alcohol and acetone. This gave 0.11 g (33%) of α-aminoethyl β-aminoethyl ketone dihydrochloride (XIV), mp 169-171°C. IR spectrum (KBr): 1720, 1595 cm^{-1}. Found: N 15.08; 14.92%. $C_5H_{14} \cdot Cl_2N_2O$. Calculated: N 14.81%.

β-Phthalimidoethyl-N-phenyl-N-acetylaminomethyl Ketone (XII). A mixture of 0.5 g of N-phenyl-N-acetylglycine (VIII) [9] and 1.35 g of (VI) in 5 ml of pyridine was heated for 5 h at 105-110° then evaporated in vacuum, the reaction product was extracted with benzene and applied to a column of Al_2O_3 of activity III.

A mixture of benzene and ethyl acetate, 1:1 eluted 0.47 g (56%) of (XII) with mp 129-131°C (ether washed). After recrystallization from water the melting point was raised to 134-136°C. The R_f was 0.74 (benzene–acetone, 1:1). IR spectrum ($CHCl_3$): 1770, 1715, 1660 cm^{-1}. Found: N 8.31; 8.36%. $C_{20}H_{18}N_2O_4$. Calculated: N 8.24%.

1-Acetonyluracil (XVIII). To a suspension of 1.7 g of uracil-1-acetic acid (I) [10] in 17 ml of pyridine 2.5 g of CH_3COCl was added while cooling with water and the mixture heated for 3 h at 90-100°C. Then a further 1 ml of CH_3COCl was introduced and the mixture was heated for 1 h at the same temperature. After cooling to ~20°C a mixture of 0.6 ml of CH_3COOH and 2 ml of CH_3COCl was added and the heating was resumed at 100-105°C (3 h). The cooled reaction mixture was diluted with water, filtered, the filtrate was evaporated to dryness, and the residue applied to a column of Al_2O_3 of activity III. The column was eluted initially with $CHCl_3$ and acetone and then with aqueous acetone (1:9) and 0.44 g (25%) of (XVIII) was eluted with mp 203-205°C (from alcohol), R_f 0.69 (acetone–water, 9:1). Found: C 49.66; 49.61; H 4.61; 4.64; N 16.77; 16.82%. $C_7H_8N_2O_3$. Calculated: C 50.00; H 4.79; N 16.65%. To a suspension of the K-salt, prepared from 1.12 g of uracil, in 15 ml of anhydrous dioxane 1.4 ml of bromoacetone was added, the mixture was boiled for 16 h, cooled, the precipitate was filtered off, and the filtrate evaporated to dryness. From the residue was isolated 0.75 g (44%) of (XVIII) with mp 202-204° by preparative TLC on Al_2O_3 activity III (acetone–water, 9:1). A solution of 1.36 g of bromoacetone in 5 ml of o-xylene was added dropwise to 1.7 g of 2,4-bis(trimethylsilylocy)pyrimidine [11] in 11 ml of boiling o-xylene, the mixture was boiled for 5 h, cooled, treated with alcohol, evaporated to dryness, and the residue chromatographed on a column of Al_2O_3, activity III. The reaction product was eluted with aqueous acetone after washing off the impurities with $CHCl_3$ and a mixture of $CHCl_3$ and $(CH_3)_2CHOH$. This gave 0.73 g (66%) of (XVIII) with mp 207-209°C.

CONCLUSIONS

1. On the basis of biochemical analogies the participation of the Dakin–West reaction is proposed in the biogenesis of those natural compounds whose molecules can be built up from an α-amino ketone grouping.

2. In order to study this amino ketone principle of synthesis of molecules of natural compounds in the examples vitamins B_1 and B_6, dihydrosphingosine, tryptamine, and uridine the Dakin–West reaction of α-N-benzoylalanine was carried out with the acid chlorides of β-ethoxypropionic, β-phthalimidopropionic, and palmitic acid, the reaction of N-acetyl-N-phenylacetic acid with β-phthalimidopropionoyl chloride, and uracil-1-acetic acid with acetyl chloride.

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