mole) of paraformaldehyde–diethylamine reagent[6] and 100 cc. of alcohol was heated in a distilling apparatus until most of the alcohol had been removed. Upon standing, the solution yielded 56.2 g. (62% based on 0.25 mole) of the yellow addition compound; m. p. 130–131°. Recrystallization from isopropyl alcohol gave 43.3 g. of product with no change in melting point.

Anal. Calcd. for $C_{17}H_{21}N_3O_6$: C, 56.19; H, 5.83. Found: C, 56.54; H, 5.81.

(b) **By the Addition of *p*-Nitrophenol to α-Diethylamino-4-nitro-*o*-cresol.**—A solution of 0.62 g. (0.00446 mole) of the former and 1 g. (0.00446 mole) of the latter in 20 cc. of alcohol was reduced in volume by evaporation. By cooling the residue, 1.46 g. (90% yield) of the addition compound resulted. Melting point and mixed melting point determinations proved its identity with a sample prepared by the Mannich reaction.

Recovery of *p*-Nitrophenol and α-Diethylamino-4-nitro-*o*-cresol from their Addition Compound.—The treatment of 7.25 g. (0.02 mole) of the yellow addition compound with 25 cc. of dilute hydrochloric acid caused a disappearance of color and a momentary solution of reactants. The white insoluble α-diethylamino-4-nitro-*o*-cresol hydrochloride soon separated. It was collected on a funnel and triturated with ether to remove *p*-nitrophenol. After recollecting and drying the material for two days at 60°, 5.27 g. (theory 5.20 g.) of crude salt was obtained; m. p. 175–215° (dec.). Recrystallized from methanol, the off-white product melted at 223–224° (dec.). The melting point was not depressed by admixture with a previously prepared sample.[3]

The ether washings were shaken in a separatory funnel with the acidic filtrate. The ether layer was washed with water and dried by washing with a saturated solution of sodium chloride. Final drying was over anhydrous magnesium sulfate. From the evaporation of the filtered ether solution, 2.5 g. (theory 2.8 g.) of *p*-nitrophenol was isolated; m. p. 109–112°. Recrystallization from benzene gave crystals which melted at 113–104°. A mixed melting point determination with recrystallized Eastman Kodak Co. white label *p*-nitrophenol indicated no depression.

α-**Diethylamino-4-nitro-*o*-cresol:** (a) **From its Hydrochloride.**—Treatment with excess ammonia of 5.2 g. (0.02 mole) of the hydrochloride, obtained by means of the Mannich reaction,[3] yielded 4.35 g. (98%) of yellow crystalline base; m. p. 88–89°. Recrystallization from isopropyl alcohol failed to change the melting point.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19. Found: C, 59.20; H, 7.30.

(b) **From α-Chloro-4-nitro-*o*-cresol.**—By following the same procedure outlined for I, 6.26 g. (80% yield) of the crude hydrochloride was obtained from 5.63 g. (0.03 mole) of α-chloro-4-nitro-*o*-cresol and 4.39 g. (0.06 mole) of diethylamine; m. p. 212–217° (dec.). Recrystallized from methanol, it melted at 224–225° (dec.)[7] and proved to be identical with the product obtained by means of the Mannich reaction.[3] Upon conversion to the free base, the compound melted at 88–90°.[8] A mixed melting point determination confirmed its identity with the Mannich base.

(6) Burckhalter, Tendick, Jones, Holcomb and Rawlins, THIS JOURNAL, **68**, 1894 (1946).

Summary

The Mannich reaction with *p*-nitrophenol and piperidine or diethylamine has been shown to lead directly to a *p*-nitrophenol addition compound of the expected α-dialkylamino-4-nitro-*o*-cresol.

p-Nitro-α-1-piperidyl-*o*-cresol and α-diethylamino-4-nitro-*o*-cresol have been prepared, and their structures have been established.

(7) Einhorn, *Ann.*, **343**, 247 (1905), using essentially the same procedure, found 197° (dec.), but failed to analyze his product.

(8) Einhorn found 68–69°.

LAWRENCE, KANSAS RECEIVED APRIL 30, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GIVAUDAN–DELAWANNA, INC.]

Adrenergic Blocking Agents. I. N-(2-Chloroethyl)-dibenzylamine Series

BY WILLIAM S. GUMP AND EDWARD J. NIKAWITZ

N-(2-Haloethyl)-dialkylamines and their salts have been described in the literature[1] and frequently used for organic syntheses. On the other hand, no information can be found in regard to the chemistry of N-(2-chloroethyl)-dibenzylamine (with the exception of a brief reference to its hydrochloride[2]) and to substituted N-(2-chloroethyl)-dibenzylamines.

In view of the known reactivity of the chlorine in the 2-chloroethyl group when the latter is attached to sulfur and nitrogen (mustard gases), it was thought that N-(2-chloroethyl)-dibenzylamine might be physiologically active and perhaps be useful therapeutically. For that reason, the hydrochloride of this amine was prepared according to the method given in Eisleb's patent. 2-Aminoethanol was condensed with benzyl chloride and the resulting 2-dibenzylaminoethanol converted into N-(2-chloroethyl)-dibenzylamine hydrochloride by means of thionyl chloride. N-(2-Bromoethyl)-dibenzylamine hydrobromide was also prepared by treatment of 2-dibenzylaminoethanol with hydrobromic acid.

The pharmacological study of N-(2-chloroethyl)-dibenzylamine (Dibenamine[3]) hydrochloride by Nickerson and Goodman[4] led to the important discovery that this compound is a potent and specific adrenergic blocking agent which inhibits and reverses the excitatory effects of epinephrine. Nickerson and Goodman's reports on Dibenamine stimulated the syntheses and

(1) Gough and King, *J. Chem. Soc.*, 2426 (1928); Slotta and Benisch, *Ber.*, **68**, 754 (1935); Amundsen and Krantz, THIS JOURNAL, **63**, 305 (1941); Huber, *et al.*, *ibid.*, **67**, 1618 (1945).

(2) Eisleb, U. S. Patent 1,949,247 (Feb. 27, 1934); see *C. A.*, **28**, 2850 (1934).

(3) Trade-mark of Smith, Kline & French Laboratories.

(4) Nickerson and Goodman, *Federation Proc.*, **5**, 194 (1946); *J. Pharmacol. Exp. Therap.*, **89**, 167 (1947).

pharmacological studies of related N-(2-chloroethyl)-amines.[5]

In order to gain information in regard to the relationship between structure and adrenergic blocking activity, a number of alkyl, methoxy, chloro and dichloro substituted N-(2-chloroethyl)-dibenzylamine hydrochlorides were synthesized, starting with alkyl-, methoxy-, chloro- and dichlorobenzyl chlorides and following the procedure as outlined for the preparation of Dibenamine hydrochloride

$$2RCH_2Cl + 3H_2NCH_2CH_2OH \longrightarrow (RCH_2)_2NCH_2CH_2OH + 2H_2NCH_2CH_2OH\cdot HCl$$

$$(RCH_2)_2NCH_2CH_2OH \xrightarrow{SOCl_2} (RCH_2)_2NCH_2CH_2Cl\cdot HCl + SO_2 + H_2O$$

R = alkyl-, methoxy-, chloro- or dichlorophenyl

The intermediate alcohols were purified by fractional vacuum distillation and obtained in yields of 50–70% as viscous, high-boiling (over 200° at 4 mm.), yellow to orange colored oils. They were converted into the corresponding N-(2-chloroethyl)-dibenzylamine hydrochlorides, the properties of which are shown in Table I. The new hydrochlorides are crystalline, white substances, practically insoluble in water, soluble in alcohols and glycols.

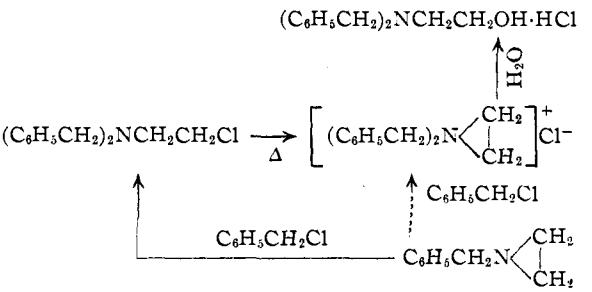
Pharmacological Results

Adrenergic blocking activity of this series of compounds was determined in anesthetized cats[6]; actual reversal of the blood pressure response to epinephrine was selected as the criterion of activity. The compounds have been listed in the table as active or inactive; the activity of Dibenamine hydrochloride (I) is designated as ++ and taken as standard for comparison. It is noted that the introduction of methyl or methoxy substituents into the aromatic rings produces little change in potency; however, compounds II and IV show a significantly decreased rate of onset of action. Substitution by chlorine or by alkyl groups larger than methyl completely abolishes adrenergic blockade, with the exception of the *m*-chloro compound (VIII) which is very slightly active.

Toxicity was tested by subcutaneous injection of the compounds into mice; the figures must be considered as approximate because of the limited number of animals which were used for each compound. The dianisyl compound (V) is considerably more toxic than the other Dibenamine derivatives; this effect of the methoxy group has been also observed in the series of N-(2-chloroethyl)-phenoxyethylamines.[7]

The 2-dibenzylaminoethanols are not adrenergic blocking substances, neither are ethers or esters of the alcohols, such as ethyl 2-dibenzylaminoethyl ether or 2-dibenzylaminoethyl benzoate.

Dibenamine hydrochloride may be converted into the free base by treating it with a cold, saturated potassium carbonate solution. The base separates as an oil which can be purified by vacuum distillation. It is fairly stable when kept at low temperatures and protected from moisture. When refluxed with water for six hours, it is completely hydrolyzed to 2-dibenzylaminoethanol hydrochloride. In view of the structural relationship of N-(2-chloroethyl)-dibenzylamine to nitrogen mustards, such as N-methyl- and N-ethyl-bis-(2-chloroethyl)-amines, it may be assumed that its transformation to the alcohol proceeds through an intermediate cyclic imonium salt as has been convincingly demonstrated for the nitrogen mustards[8] and for diethylamino- and dibenzylaminochloropropanes.[9]



Attempts to obtain the ethylenimonium intermediate by treatment of N-benzylethylenimine with benzyl chloride failed; the end-product was always N-(2-chloroethyl)-dibenzylamine.

Experimental

2-Dibenzylaminoethanol.—2-Aminoethanol (122 g., 2 moles) was stirred, heated to about 40°, and 257 g. (2 moles) of benzyl chloride was added, dropwise. At first, the addition of the benzyl chloride was regulated so that the temperature of the mixture rose to about 100°. Later, external heat was applied to keep the temperature at 100–110° until all of the chloride had been added. After the mixture had been heated and stirred at 100–110° for two and one-half hours, a solution of 80 g. of sodium hydroxide in 120 ml. of water was added slowly, and the mixture was stirred at 100° for one hour. The oil was extracted from the cold mixture with 200 ml. of benzene, the benzene solution washed with 200 ml. of water, and then dried with anhydrous sodium sulfate. The product boiled at 190–

(5) Rieveschl, Fleming and Coleman, Abstracts of Papers, 112th Meeting, A. C. S., Sept. 1947, p. 17K; Achenbach and Loew, *Federation Proc.*, **6**, 304 (1947); Loew, Micetich and Achenbach, *ibid.*, **6**, 351 (1947); Loew and Micetich, *J. Pharmacol. Exp. Therap.*, **93**, 434 (1948); **94**, 339 (1948); Achenbach and Loew, *ibid.*, **95**, 448 (1949); Hunt, *ibid.*, **95**, 177 (1949); Kerwin and Ullyot, Abstracts of Papers, 115th Meeting, A. C. S., March 1949, p. 10K; Kerwin, *et al.*, *Federation Proc.*, **8**, 308 (1949); Ullyot, *et al.*, *ibid.*, **8**, 340 (1949); Henderson and Chen, *ibid.*, **8**, 301 (1949); see also Nickerson, "Pharmacological Reviews," *J. Pharmacol. Exp. Therap.*, **95**, 27 (part 2, April 1949).

(6) The authors are greatly indebted to Dr. M. Nickerson of the University of Utah for the pharmacological tests of these compounds. A detailed report of these tests has been published elsewhere [Nickerson and Gump, *J. Pharmacol. Exp. Therap.*, **97**, 25 (1949)].

(7) Unpublished data.

(8) Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518 (1946); Fruton and Bergmann, *ibid.*, **11**, 543 (1946); Golumbic, Stahmann and Bergmann, *ibid.*, **11**, 550 (1946).

(9) Kerwin, *et al.*, THIS JOURNAL, **69**, 2961 (1947).

TABLE I

N-(2-CHLOROETHYL)-DIBENZYLAMINE HYDROCHLORIDES, $(RCH_2)_2NCH_2CH_2Cl \cdot HCl$

R = mono- or disubstituted phenyl

No.	Substituent in phenyl group	Empirical formula	M. p.,[a] °C.	Yield,[b] %	Analyses, % chlorine: Chloride Calcd.	Chloride Found	Total Calcd.	Total Found	Toxicity[c] (approx. L. D. 50), mg./kg.	Adrenergic blocking activity[c]
I	.....	$C_{16}H_{19}NCl_2$	194–195[d]	68	12.0	12.1	24.0	24.1	800	++
II	*o*-Methyl	$C_{18}H_{23}NCl_2$	180–182	62	11.0	11.1	21.9	22.1	1000	++ (slow)
III	*m*-Methyl	$C_{18}H_{23}NCl_2$	157–159	31	11.0	10.9	21.9	21.8	1000	++
IV	*p*-Methyl	$C_{18}H_{23}NCl_2$	169–171	57	11.0	11.1	21.9	21.9	1000	++ (slow)
V	*p*-Methoxy	$C_{18}H_{23}O_2NCl_2$	133–136	23	10.0	10.0	20.0	20.2	300	++
VI	*p*-Ethyl	$C_{20}H_{27}NCl_2$	148–150	39	10.2	10.4	20.2	20.2	>1000	−
VII	*p*-Isopropyl	$C_{22}H_{31}NCl_2$	195–197	70	9.4	9.5	18.7	19.0	>1000	−
VIII	*m*-Chloro	$C_{16}H_{17}NCl_4$	178–179	68	9.7	9.9	38.9	39.1	>1000	+ (v. slight)
IX	*p*-Chloro	$C_{16}H_{17}NCl_4$	189–191	61	9.7	10.0	38.9	38.8	>1000	−
X	*o,p*-Dichloro	$C_{16}H_{15}NCl_6$	151–152	77	8.2	8.4	49.1	48.8	>1000	−
XI	*m,p*-Dichloro	$C_{16}H_{15}NCl_6$	192–194	75	8.2	8.5	49.1	49.2	>1000	−
							Br	Br		
XII	.....[e]	$C_{16}H_{19}NBr_2$	177–179	40			41.6	41.6	500	+++

[a] All melting points are corrected. [b] Yields are based on 2-dibenzylaminoethanols. [c] See text for explanation. [d] Ref. 2; m. p. 192°. [e] N-(2-Bromoethyl)-dibenzylamine hydrobromide.

195° (5 mm.)[10] and congealed at 44°[10]; yield 161 g. (67%).

In order to prepare the hydrochloride, a cold solution of the 2-dibenzylaminoethanol in absolute alcohol was treated with hydrogen chloride and the salt then precipitated with ether. After two recrystallizations from alcohol, the hydrochloride melted at 183–184°.[11]

Anal. Calcd. for $C_{16}H_{20}NOCl$: Cl, 12.8. Found: Cl, 12.7.

The substituted 2-dibenzylaminoethanols were prepared in a similar manner from *o*-,[12] *m*-[13] and *p*-xylyl bromide,[12] anisyl chloride,[14] *p*-ethyl[15] and *p*-isopropyl chloride,[15] *p*-chloro,[16] *o,p*-dichloro[16] and *m,p*-dichlorobenzyl chloride,[16] and *m*-chlorobenzyl bromide.[17]

2-Dibenzylaminoethyl Benzoate Hydrochloride.—A mixture of 25.7 g. (0.1 mole) of 2-dibenzylaminoethanol, 21 g. (0.15 mole) of benzoyl chloride and 100 ml. of benzene, after twenty-four hours, was evaporated to dryness, and the residue recrystallized from alcohol; yield 18 g. (47%); m. p. 215–217°.[18]

Anal. Calcd. for $C_{23}H_{24}NO_2Cl$: C, 72.35; H, 6.34. Found: C, 72.36; H, 6.31.

Ethyl 2-Dibenzylaminoethyl Ether Hydrochloride.—Fifty-nine grams (0.2 mole) of N-(2-chloroethyl)-dibenzylamine hydrochloride was added in small portions to a stirred solution prepared from 9.2 g. (0.4 mole) of sodium and 200 ml. of absolute alcohol. The mixture was refluxed for fifteen hours, filtered, the alcohol removed under reduced pressure and the residue distilled; b. p. 165–167° (4 mm.).

The oil (27 g.) was dissolved in dilute hydrochloric acid, the solution evaporated to dryness and the residue recrystallized twice from alcohol–ether; m. p. 116–118°; yield 15 g. (25%).

Anal. Calcd. for $C_{18}H_{24}NOCl$: C, 70.59; H, 7.91. Found: C, 70.61; H, 7.83.

N-(2-Chloroethyl)-dibenzylamine (Dibenamine) Hydrochloride (I).—A solution of 241 g. (1 mole) of dibenzylaminoethanol in 250 ml. of chloroform was cooled in an ice-bath, stirred and a solution of 138 g. (1 mole) of thionyl chloride in 150 ml. of chloroform was added during two hours. The mixture was stirred for three hours at 15–25°. After twelve hours at room temperature the chloroform was removed under reduced pressure and the residue recrystallized from ethanol and decolorized with the aid of charcoal; yield 162 g.; m. p. 194–195°. Addition of ether to the mother liquor yielded an additional 40 g.; m. p. 192–194°; total yield 68%.

The substituted N-(2-chloroethyl)-dibenzylamine hydrochlorides (Table I) prepared in a similar manner, were recrystallized once or twice from alcohol–ether. In the case of compounds V and VI, the reaction products were first isolated as soft brown resins; they became partly crystalline when kept in the refrigerator for a period of one to two weeks, and could then be purified by two recrystallizations from alcohol–ether.

N-(2-Bromoethyl)-dibenzylamine Hydrobromide (XII).—Melted 2-dibenzylaminoethanol (48 g.) was slowly added to 90 ml. of ice-cold hydrobromic acid (d. 1.42). The mass became solid, and another 90 ml. of hydrobromic acid was added. The mixture was refluxed for three hours and about 50 ml. of liquid was then removed by distillation. After the mixture had been refluxed for an additional three hours, it was concentrated to about 50 ml. and extracted with ether. The aqueous layer was evaporated to dryness under reduced pressure and the residue recrystallized twice from alcohol–ether; yield 38 g. (40%); m. p. 177–179°.

N-(2-Chloroethyl)-dibenzylamine.—Thirty grams of finely powdered N-(2-chloroethyl)-dibenzylamine hydrochloride was stirred vigorously for a half hour with 50 ml. of a saturated aqueous solution of potassium carbonate. The mixture was extracted with 50 ml. of benzene. The benzene layer was dried with anhydrous sodium sulfate and after removal of the solvent the residual oil distilled. The oily, yellow product boiled at 182–184° (5 mm.); $n^{20}D$ 1.5655.

Anal. Calcd. for $C_{16}H_{18}NCl$: Cl, 13.7. Found: Cl, 13.6.

N-Benzylethylenimine.—This base was obtained from 2-benzylaminoethanol[19] which was prepared by reductive

(10) (a) Ref. 2, b. p. 175° (3 mm.), m. p. 46–47°; (b) Gabel, *Bull. soc. chim.*, [5] **1**, 1006 (1934), b. p. 220–225° (23 mm.), m. p. 45.5–47°; (c) Rumpf and Kwass, *ibid.*, [5] **10**, 347 (1943), b. p. 220–225° (25 mm.), m. p. 48°.

(11) Ref. 10b, m. p. 173°.

(12) Eastman Kodak Company.

(13) Atkinson and Thorpe, *J. Chem. Soc.*, **91**, 1696 (1907).

(14) Cannizzaro and Bertagnini, *Ann.*, **98**, 191 (1857); Shriner and Hull, *J. Org. Chem.*, **10**, 228 (1945).

(15) Blanc, *Bull. soc. chim.*, [4] **33**, 313 (1923).

(16) Heyden Chemical Corp.

(17) Oxford and Robinson, *J. Chem. Soc.*, 2241 (1927).

(18) Gabel (ref. 10b) reported 168–169° as the melting point but when we refluxed 2-dibenzylaminoethanol with benzoyl chloride in benzene solution, according to his procedure, 2-dibenzylaminoethanol hydrochloride, m. p. 172–174°, instead of the benzoate hydrochloride, was obtained.

(19) Gabriel and Stelzner, *Ber.*, **29**, 2381 (1896).

amination of benzaldehyde with 2-aminoethanol according to the procedure of Cope and Hancock[20] for 2-alkylaminoethanols.

The cyclization of 2-benzylaminoethanol was carried out following the method described by Wenker[21] and by Leighton, Perkins and Renquist[22] for the preparation of ethylenimine from 2-aminoethanol. The intermediate 2-benzylaminoethylsulfuric acid could not be purified by trituration with ethanol as it was too soluble in this solvent; the crude product was used directly for the decomposition with the sodium hydroxide solution. The N-benzylethylenimine was obtained as a colorless liquid; b. p. 84–87° (8 mm.); $n^{20}D$ 1.5300; yield 24%.

Anal. Calcd. for $C_9H_{11}N$: C, 81.14; H, 8.34. Found: C, 80.82; H, 8.41.

(20) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).
(21) Wenker, *ibid.*, **57**, 2328 (1935).
(22) Leighton, Perkins and Renquist, *ibid.*, **69**, 1540 (1947).

Acknowledgment.—The authors are indebted to Dr. James C. Vitucci for technical assistance in part of this work.

Summary

A series of substituted N-(2-chloroethyl)-dibenzylamine hydrochlorides has been prepared and tested as adrenergic blocking agents.

Substituents in the phenyl rings, other than methyl, greatly diminish or completely abolish the adrenergic blocking activity shown by N-(2-chloroethyl)-dibenzylamine (Dibenamine) hydrochloride.

DELAWANNA, NEW JERSEY RECEIVED JULY 11, 1949

[CONTRIBUTION FROM THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, DEPARTMENT OF CHEMISTRY]

Peptide Syntheses Using Energy-rich Phosphorylated Amino Acid Derivatives*

JOHN C. SHEEHAN AND VICTOR S. FRANK[1]

The synthesis of peptides and of peptide-like substances is known to take place with ease in living systems. For example, Borsook and Dubnoff[2] have shown that hippuric acid is formed rapidly in liver tissue supplied with glycine and benzoic acid in very dilute solution. However, it has been calculated from thermodynamic data that the change in free energy (ΔF) for this reaction is +2560 calories.[3] Expressed in terms of the equilibrium constant K, this corresponds to a value of approximately 10^{-2}. Consequently, hippuric acid would be more than 99% hydrolyzed at equilibrium under the conditions of the biosynthesis.

In a discussion of the free energy requirements for the synthesis of peptides *in vivo*, Borsook and Huffman[3] point out that equilibria involving peptides and their constituent amino acids would also lie well over on the side of hydrolysis. The synthesis of a typical peptide such as leucylglycine from the amino acids would be attended by a positive free energy change (ΔF = +2930 calories for leucylglycine). Since ΔF for the over-all process must be negative, the formation of a peptide bond in nature must be associated with another free energy-yielding reaction. In the currently accepted theory of the biogenesis of proteins, the driving force for the synthesis is attributed to the free energy supplied by intermediate phosphorylated compounds. The rupture of a "high-energy phosphate bond" is strongly "exergonic"[4] (ΔF about −11,000 calories for hydrolysis).[4,5,6] Compounds containing this high energy linkage are anhydrides or analogs of anhydrides. For example, the mixed anhydrides of phosphoric acid with acetic and glyceric acids are high energy compounds. Pyrophosphates are also high energy compounds. An example is adenosine triphosphate. Phosphorylated enols (*e. g.*, "phosphoenolpyruvic acid") and guanidino phosphates also contain high energy phosphate bonds. Examples of the latter type are phosphorylated creatine and arginine.

Phosphorylated compounds have been recognized as important intermediates in the synthesis of polysaccharides and in various fermentation processes.[5] Phosphoric acid derivatives are known to be responsible for the storage and transfer of energy in many cellular reactions.

The functions of phosphorylated compounds in metabolic processes have been reviewed by Lipmann.[6] This author has discussed the role of "energetic coupling reactions" in biological syntheses and has implied that the origin of the peptide bond in living cells may be ascribed to energy-rich acyl phosphates related to amino acids.

It was later definitely proposed by Lipmann[7] and by Cohen and McGilvery[8] that the potential energy required for peptide bond formation may be supplied by acyl phosphates. A recent publication of Chantrenne[9] suggests that the high-energy

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(1) Swift Amino Acid Fellow, 1947–1949. Present address: Research Department, Merck and Co., Inc., Rahway, N. J.

(2) Borsook and Dubnoff, *J. Biol. Chem.*, **132**, 307 (1940).

(3) Schmidt, "The Chemistry of the Amino Acids and Proteins," C. C. Thomas, Springfield, Ill., 1945. Chapter XV by Borsook and Huffman includes some thermodynamical considerations of peptide synthesis.

(4) Kalckar, *Chem. Revs.*, **28**, 71 (1941).

(5) Green and Colowick, *Ann. Rev. Biochem.*, **13**, 155 (1944). This review discusses many of the processes which involve phosphorus compounds, in addition to methods for their chemical and biological preparation.

(6) Lipmann, *Adv. in Enzymology*, **1**, 99 (1941).

(7) Lipmann, *ibid.*, **6**, 231 (1946).

(8) Cohen and McGilvery, *J. Biol. Chem.*, **166**, 261 (1946); **169**, 199 (1947).

(9) Chantrenne, *Nature*, **160**, 603 (1947).