Let c = fraction IX formed through path C, then (0.97 − c) is the fraction of IX formed through path E.

$$0.508 = c + \frac{0.97}{2} - c \text{ (Table II)}; \quad c = 0.046$$

$m_c = 0.046 \times 0.516 = 0.024$

$m_e = 0.476$ and $m_d = 0.474$

Method 2.—The ratio of IX/X from rearrangement of VI = 0.961 (Table I). Therefore $m_d \times 0.961 = m_e = 0.455$ and $m_c = 0.500 - 0.455 = 0.045$.

(b) **For *erythro*-VII; Method 1.**—The *erythro*-glycol has 68% of its carbon-14 in the 1-position and 32% in the 2-position. From Table II, x = fraction of rearrangement in X. Therefore

$$0.32x \times 0.68\,(1 - x) = 0.574$$
$$x = 0.295$$

y = fraction of rearrangement in IX, then

$$0.32y + 0.68\,(1 - y) = 0.66$$
$$y = 0.056$$

$m_a + m_d = 0.546$; $m_b + m_e = 0.454$

$m_a = 0.295 \times 0.546 = 0.161$;

$m_b = 0.056 \times 0.454 = 0.0254$

$m_d = 0.385$

$m_c + m_e = 0.429$

$m_e = m_d \times 1.004 = 0.387$; thus $m_c = 0.042$

Method 2

$m_e = m_d = 0.961 = 0.370$; thus $m_c = 0.059$

(c) **For VIII; Method 1**

$m_f + m'_d = 0.600$ (Table I)

$m'_e = 0.400$; $m'_d = \frac{0.400}{1.004} = 0.397$ and $m_f = 0.203$

Method 2

$m'_d = \frac{0.400}{0.961} = 0.416$ and $m_f = 0.184$

Preparation and Rearrangement of Tri-*p*-tolylethylene Glycol.—In a typical run, 10 g. of 4,4′-dimethylbenzoin[27] in 150 cc. of ether was added to the Grignard reagent prepared from 21.4 g. of *p*-bromotoluene and 3.0 g. of magnesium turnings. After addition was complete the mixture was heated under reflux for 4.5 hours, then poured over ice to which had been added saturated, aqueous ammonium chloride solution. The crude glycol was obtained through ether extraction and weighed 8 g. (61% of theory). Upon crystallization from ethanol followed by crystallization from hexane there was obtained 5.9 g. of white needles, m.p. 161°.

Anal. Calcd. for $C_{23}H_{24}O_2$: C, 83.1; H, 7.29. Found: C, 83.27, 83.48; H, 7.31, 7.29.

In an analogous experiment 9.5 g. of 4,4′-dimethylbenzoin,[27] 2.6 g. magnesium turnings and 16.9 g. of *p*-bromotoluene-*methyl*-C^{14})-tri-*p*-tolylethylene glycol, m.p. 161.5°; radioactivity assay, 3.387 ± 0.017 mc./mole.

For the preparation of chain-labeled 1,1,2-tri-*p*-tolylethylene glycol, chain-labeled 4,4′-dimethylbenzoin and non-radioactive *p*-bromotoluene were employed to yield a product whose m.p. was 161.5°, and whose radioactivity assay was 1.871 ± 0.012 mc./mole. Oxidation of this glycol with chromic acid yielded *p*-toluic acid, 0.1089 ± 0.0002 mc./mole, and di-*p*-tolyl ketone, whose 2,4-dinitrophenylhydrazone had a m.p. of 221° and a radioactivity assay of 1.752 ± 0.003 mc./mole, corresponding to 94.15% carbon-14 in the 1-position and 5.85% carbon-14 in the 2-position.

The foregoing isotope position isomers of 1,1,2-tri-*p*-tolylethylene glycol were subjected to rearrangement in cold concentrated sulfuric acid as described for compounds VI, VII and VIII. The products were dissolved in hexane and passed through alumina to yield 60–80% of α-*p*-tolyl-4,4′-dimethyldesoxybenzoin, a viscous oil which was characterized by alkaline cleavage to *p*-toluic acid and di-*p*-tolylmethane. The latter fractions were oxidized with chromic acid in acetic acid to the di-*p*-tolyl ketones which were converted to 2,4-dinitrophenylhydrazones. The degradation products from oxidation of the tolyl-labeled ketone were: toluic acid, m.p. 176°, 1.145 ± 0.004 mc./mole; di-*p*-tolyl ketones 2,4-dinitrophenylhydrazone, m.p. 220°, 2.188 ± 0.016 mc./mole. The degradation products from oxidation of the chain-labeled ketone were: toluic acid, m.p. 176°, 0.1888 ± 0.0005 mc./mole, and di-*p*-tolyl ketone 2,4-dinitrophenylhydrazone, m.p. 221°.

Calculation of k_{Tol}/k'_H Ratio for the Rearrangement of Tri-*p*-tolylethylene Glycol.—These calculations are carried out in an analogous fashion to those previously reported (ref. 3, Chart I) for the rearrangement of triphenylethylene glycol. Let x be the fraction of secondary hydroxyl removal (corresponding to path 1 in ref. 3), then (1 − x) represents the fraction proceeding through tertiary hydroxyl removal. Then $0.9415x + 0.0585(1 - x) = 0.1015$ and $x = 0.0487$. In order to calculate a *minimum* value for k_{Tol}/k'_H we assume that only the unlabeled tolyl group migrates to the secondary carbonium ion. Thus let y correspond to path 2 (ref. 3) then (0.951 − y) corresponds to path 4 and

$$y + \frac{(0.951 - y)}{3} = 0.656$$

$y = 0.0645$; $(0.951 - y) = 0.887$

and

$$\frac{k_{Tol}}{k'_H} = \frac{0.887}{0.0645} = 14$$

OAK RIDGE, TENNESSEE

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE STATE UNIVERSITY]

Nitrogen Analogs of Ketenes. IV.[1] Reactions with Carboxylic Acids

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The nitrogen analogs of ketenes react readily with carboxylic acids to form imides in good yield. The dicarboxylic acids, phthalic and succinic, form the acid anhydride when treated with a ketenimine. The structure of one of the unsymmetrical imides was proved by independent synthesis and infrared analysis. Evidence was obtained that the reaction of ketenimines with carboxylic acids proceeded *via* an intermediate that was a more active acylating agent than the imide. This intermediate is considered to be the isoimide. The imides were shown to be acylating agents for alcohols, aliphatic amines and aromatic amines. The attack of a nucleophilic agent upon an unsymmetrical imide was shown to be subject to steric control.

Staudinger published the first study of nitrogen analogs of ketenes in 1920[4] and 1921.[5] The ketenimines were prepared by reaction of a ketene with a phosphinimine or an isocyanate with a phosphine-

(1) Part III is in THIS JOURNAL, **79**, 6057 (1957).

(2) Abstracted from the dissertation submitted by M. E. Munk in partial fulfillment of the requirement for the degree of Doctor of Philosophy, Wayne State University, 1957.

(3) National Science Foundation Fellow, 1954–1955; Ethyl Corporation Fellow, 1955–1956.

(4) H. Staudinger and J. Meyer, *Ber.*, **53B**, 72 (1920).

(5) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 887 (1921).

methylene. Backer[6] reported the preparation of ketenimines by reaction of diazomethane with negatively substituted acetonitriles. Recently two new methods for the rapid and convenient preparation of a variety of ketenimines were reported from this Laboratory[7] and the present paper reports a study of the reaction of the ketenimines with carboxylic acids.

Diphenylketene-N-*p*-tolylimine(I) reacted readily with acetic acid, benzoic acid and diphenylacetic acid in benzene solution to give 76, 87 and 80%, respectively, of the corresponding imide III. In an early study of unsymmetrical imides, Mumm[8] showed that reactions designed to produce the isoimide or imino anhydride structure II gave only compounds of structure III. In the structural determination work of this investigation, one example of III (R = CH_3) was synthesized by acylation of two different amides. Diphenylacetic acid *p*-toluide was acetylated *via* the sodium salt to give III (R = CH_3) and the sodium salt of acetic acid *p*-toluide was diphenylacetylated to give the same product. The fact that these two reactions produced the same material indicated that the structure of the product is III since if O-acylation had occurred in either case at least one other isomer should have been formed. Mumm[8] assigned the imide structure from the fact that a pair of imino chlorides reacted with the appropriate pair of carboxylic acid sodium salts to give the same product. Compound III was also prepared by the reaction of Mumm[8] from IV and is the fourth reaction for the formation of III (R = CH_3).[9]

Further evidence for the imide structure for III appeared in the infrared spectra. The adduct from acetic acid III (R = CH_3) had a characteristic doublet in the carbonyl region at 5.80 and 5.85 μ, the benzoic acid adduct III (R = C_6H_5) had a doublet at 5.83 and 5.88 μ, and the diphenylacetic acid had a doublet at 5.82 and 5.86 μ. The bands correspond well with those reported by Witkop[10] (5.80 and 5.84 μ) and Sheehan[11] (5.80 and 5.85 μ) for diacyl amides. Witkop[10] also reported other examples which varied little and all of these examples had the doublet bands approximately the same distance apart: Δ0.05 μ, Δ15 cm.$^{-1}$. The two carbonyl bands of anhydrides vary in position depending upon whether the carbonyl groups are conjugated or unconjugated, part of a strained five-membered ring or part of an open chain system, but the bands are always approximately the same distance apart[12]: Δ60 cm.$^{-1}$, Δ0.20 μ.

As model compounds for the imino anhydride structure IIa, the known azlactone V and the phthalic imino anhydride VI were prepared and the infrared spectrum compared with those of III. Each spectrum had two bands in the carbonyl region; V absorbed at 5.48 and 5.92 μ and VI absorbed at 5.56 and 5.84 μ. The position of the bands is not meaningful since the imino anhydride structure is incorporated into a strained five-membered ring in both examples, but the fact that the distance between the bands is Δ136 cm.$^{-1}$, Δ0.44 μ in one example and Δ87 cm.$^{-1}$, Δ0.28 μ in the other supports the imide structure for III.

In the reaction of the ketenimine I with carboxylic acids to give III, the existence of an intermediate was demonstrated in the following way. The ketenimine I was dissolved in *glacial* acetic acid at room temperature. Within 15 minutes 77% of amide VII was formed and the presence of acetic anhydride in the acetic acid was apparent from spectroscopic data. Imide III was formed in the amount of 13%. The crystalline acetic acid adduct III (R = CH_3) was dissolved in glacial acetic acid

$$I + CH_3COOH \longrightarrow II + CH_3COOH \longrightarrow CH_3COOCOCH_3 + (C_6H_5)_2CHCONHC_6H_4CH_3 \text{ (VII)}$$

and after nine hours 96% of the starting material could be recovered by dilution of the reaction mixture with water.

From these data compound I was considered to react with acetic acid to give II, which in the presence of a high concentration of the polar acetic acid was able to acylate the acetic acid (77%) by a bimolecular reaction before an appreciable amount (13%) of intramolecular rearrangement product was formed. The formation of good yields of III with one equivalent of acetic acid in dilute nonpolar solution is consistent with this view. The intermediate is clearly a more active acylating agent than III.

The imino anhydride intermediate II could not be isolated from the reaction of the hindered mesitoic acid and the ketenimine I; only the imide III (R = mesityl) was the product. Highly hindered carbonyl groups have been shown to undergo intramolecular reactions, the intermolecular analogs of which could not be realized.[13]

With phthalic and succinic acid the product of reaction with I was the anhydride in 87 and 47% yield, respectively. On the basis of the previous experiments, the anhydride formation undoubtedly proceeded by initial reaction of one carboxylic acid group with the ketenimine to give the imino anhydride VIII, followed by *intramolecular* acylation to give the amide and the anhydride. However, an attempt to disprove the alternate mechanism involving rearrangement to IX prior to acylation failed; IX was prepared independently by hydrogenolysis of the benzyl ester. From the hydrogenation mixture only anhydride could be obtained, which showed that intramolecular acylation of an acid by an imide proceeded readily while the corresponding bimolecular acylation of acetic acid by III did not take place, even in pure acetic acid.

Although the imides III were not able to acylate acetic acid at room temperature, they were rela-

(6) R. Dijkstra and H. J. Backer, *Rec. trav. chim.*, **73**, 575, 695 (1954).

(7) C. L. Stevens and J. C. French, THIS JOURNAL, **75**, 657 (1953); **76**, 4398 (1954).

(8) O. Mumm, H. Hesse and H. Volquartz, *Ber.*, **48**, 388 (1915).

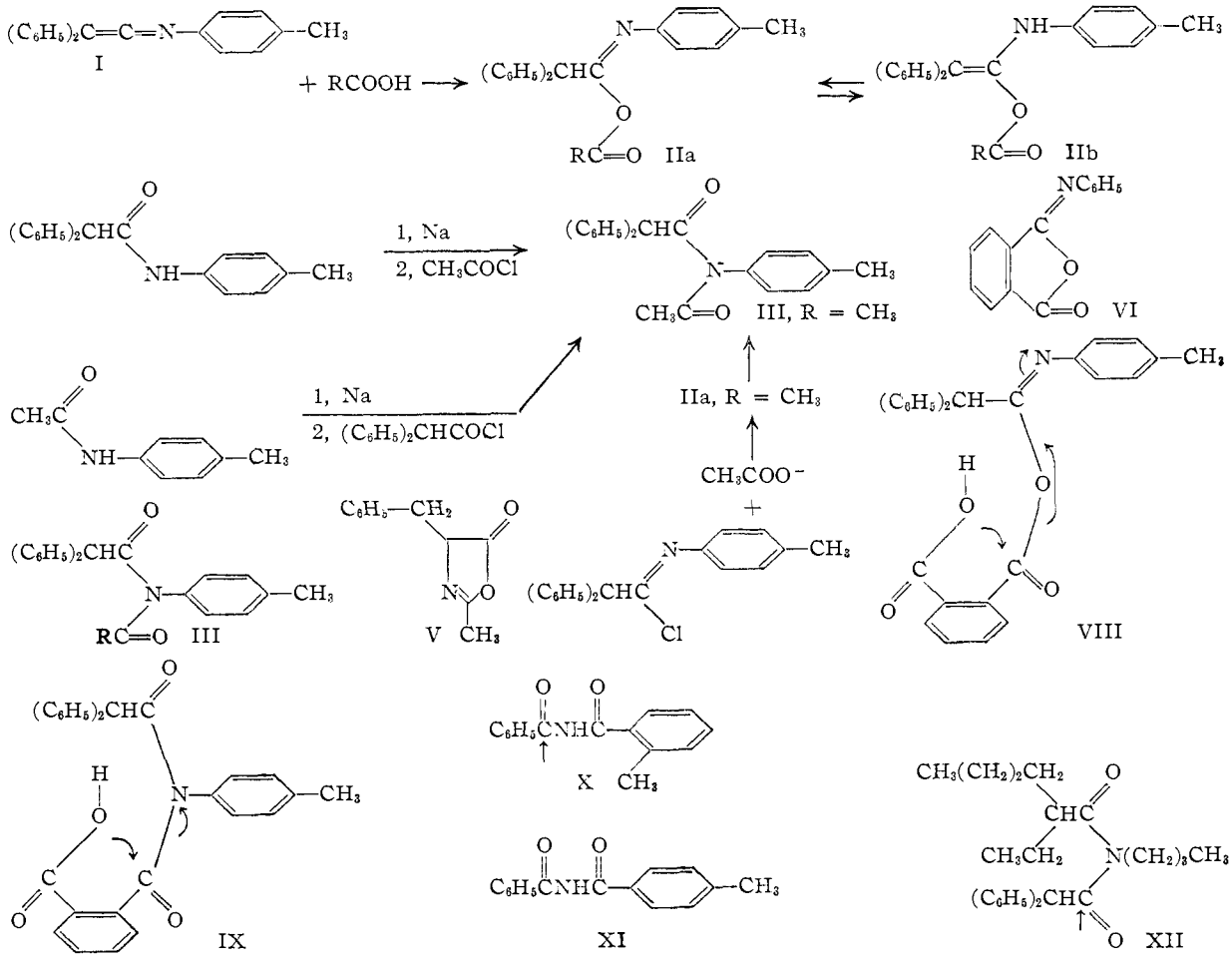
(9) However, these reactions do not rigorously prove the structure of III (R = CH_3) since in the unlikely event that one of the two O-acyl amides was the most stable of the three isomers, the other O-acyl amide isomer and the imide could conceivably rearrange to it by O to N and/or N to O acyl migrations, no matter which is the initial product of reaction.

(10) B. Witkop and J. B. Patrick, THIS JOURNAL, **74**, 3861 (1952).

(11) J. C. Sheehan and E. J. Corey, *ibid.*, **74**, 360 (1952).

(12) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 110.

(13) R. C. Fuson and W. C. Hammann, THIS JOURNAL, **74**, 1626 (1952). A. Wohl observed in 1910 (*Ber.*, **43**, 3476 (1910)) that intramolecular rearrangements are not significantly influenced by steric effects.



tively active acylating agents. Base-catalyzed alcoholysis of III proceeded to give 61% of the *p*-toluide VII of diphenylacetic acid. More important was the ability of the imides to acylate amines. Treatment of III (R = CH_3) with one equivalent of N-butylamine in hexane gave 92% of the amide VII and 60% of N-butylacetamide. *p*-Toluidine was acetylated by the symmetrical adduct III (R = $(C_6H_5)_2CH$) to give 61% of N-*p*-tolyldiphenylacetamide (VII).

With the unsymmetrical imide III (R = CH_3) the nucleophilic agents attacked the acetyl carbonyl in preference to the diphenylacetyl carbonyl. The reactions of unsymmetrical imides have been studied recently by Wieland[14] who lists the order of reactivity as acetyl > propionyl > butyryl > benzoyl. In 1914, Titherley[15] found that N-benzoyl-*o*-toluoamide (X) was hydrolyzed by hot or cold basic solution to give complete attack on the benzoyl carbonyl with the formation of benzoic acid and *o*-toluic amide. Hydrolysis of the *p*-isomer XI cold gave mostly benzoic acid, hot gave about half benzoic acid and half *p*-toluic acid. These data indicate electronic and steric effects can be used to direct the attack of nucleophilic agent to a particular carbonyl group.

To test the steric influence ethylbutylketene N-butylimine was allowed to react with diphenylacetic acid and the resulting imide XII used to acylate *p*-toluidine. The isolation of VII in 27% yield showed the ethyl and butyl groups to effectively hinder attack on the caproyl carbonyl.[16]

The rearrangement of II to III must involve an intramolecular O to N acyl migration *via* a four-membered ring transition state. Although the number of such rearrangements recorded in the literature is not large, one closely related example occurs in the reaction of a carbodiimine with a carboxylic acid to give an acylurea.[17] The reaction of an isocyanate with a carboxylic acid to give an amide and carbon dioxide[18] and the reaction of an isothiocyanate with a thiol acid to give an amide and carbon disulfide[19] involve two other very similar O to N acyl migrations.

Experimental

Addition of Carboxylic Acids to Diphenylketene-*p*-tolylimine.—A solution of 2.0 g. (7.05 millimoles) of diphenylketene-*p*-tolylimine (I) and 4.0 g. (66 millimoles) of glacial acetic acid in 100 ml. of dry benzene was refluxed until the yellow color of the ketenimine was completely discharged.

(14) T. Wieland and H. Mohr, *Ann.*, **599**, 222 (1956).

(15) A. W. Titherley and L. Stubbs, *J. Chem. Soc.*, **105**, 299 (1914).

(16) *Cf.* M. S. Newman, THIS JOURNAL, **72**, 4783 (1950).

(17) F. Zetzsche, *et al.*, *Ber.*, **71**, 1089 (1938), and subsequent papers; J. C. Sheehan and G. P. Hess, THIS JOURNAL, **77**, 1067 (1955); H. G. Khorana, *Chemistry & Industry*, 1087 (1955).

(18) C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1935); S. Goldschmidt and M. Wick, *Ann.*, **575**, 217 (1952).

(19) H. L. Wheeler and H. F. Merriam, THIS JOURNAL, **23**, 283 (1901); J. von Braun, *Ber.*, **63**, 3520 (1903); J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, **21**, 404 (1956).

The benzene solution was washed carefully twice with 5% sodium bicarbonate solution and once with water. The benzene solution was dried and evaporated under reduced pressure and the resulting oil was crystallized from petroleum ether (50–60°) to yield 1.82 g. (76%) of a N-acetyldiphenylacetic acid *p*-toluide (III, R = CH_3), m.p. 97–98.5°. Two additional recrystallizations from petroleum ether (50–60°) raised the melting point to 98–99°.

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.41; H, 6.16. Found: C, 80.43; H, 6.26.

Addition of benzoic acid to I gave 87% of N-benzoyldiphenylacetic acid *p*-toluide (III, R = C_6H_5), m.p. 125–126°.

Anal. Calcd. for $C_{28}H_{23}NO_2$: C, 82.91; H, 5.72. Found: C, 82.92; H, 5.95.

The adduct from diphenylacetic acid and I, N-*p*-tolyldiphenylacetimide (III, R = benzhydryl), was obtained in 80% yield, m.p. 118–120°.

Anal. Calcd. for $C_{35}H_{29}NO_2$: C, 84.81; H, 5.90. Found: C, 84.87; H, 6.00.

The mesitoic acid adduct was prepared in 65% yield, m.p. 107–109°.

Anal. Calcd. for $C_{31}H_{29}NO_2$: C, 83.17; H, 6.53; N, 3.13. Found: C, 83.57; H, 6.47; N, 3.39.

N-Acetyldiphenylacetic Acid *p*-Toluide (III, R = CH_3).—Into a three-necked flask fitted with stirrer, gas inlet tube, condenser and drying tube was introduced 11.40 g. (0.038 mole) of diphenylacetic acid *p*-toluide suspended in 200 ml. of dried toluene. Dry nitrogen was passed through the system and then 1.75 g. (0.038 g. atom) of a 50% sodium dispersion in toluene diluted with an additional 25 ml. of dried toluene was added. The contents were heated at the reflux temperature until the gray sodium color was completely discharged. After the reaction had cooled to room temperature, 3.18 g. (0.04 mole) of freshly distilled acetyl chloride in 25 ml. of dried toluene was added and the contents stirred at room temperature for 2 hours. The white precipitate, a 97% yield of sodium chloride, was filtered and the toluene evaporated under reduced pressure. The resulting oil was crystallized from petroleum ether (30–60°) to yield a white solid, m.p. 96–98°. Recrystallization from petroleum ether (30–60°) produced 5.5 g. (43%) of III, (R = CH_3), m.p. 98–100°. A mixture melting point with the acetic acid adduct of the ketenimine I was not depressed.

Following the same procedure, 14.5 g. (0.076 mole) of acetic acid *p*-toluide was acylated with 18.0 g. (0.078 mole) of diphenylacetyl chloride to produce 16.2 g. (62%) of a white crystalline solid, m.p. 97–99°. A mixture melting point with either the product above or the acetic acid adduct of the ketenimine I was not depressed.

The same product was obtained from sodium acetate and the iminochloride. A stream of dry hydrogen chloride was passed into a solution of 0.5 g. (1.76 millimoles) of diphenylketene-*p*-tolylimine (I) in 65 ml. of dried ether until the yellow color of the ketenimine I was discharged completely. The contents were cooled to −10° and a cold solution (−10°) of 1.45 g. (0.0176 mole) of anhydrous sodium acetate in 30 ml. of glacial acetic acid was added with stirring. After stirring at −10° for 36 hours the suspension was washed twice with cold water. Evaporation of the clear, colorless ether layer under reduced pressure without the application of heat produced 0.55 g. (91%) of a white crystalline solid, m.p. 93.5–95.0°. Recrystallization from petroleum ether raised the melting point to 98–100°. A mixture melting point with III (R = CH_3) made above was not depressed, m.p. 98–100°.

The iminochloride could be isolated in 55% yield after addition of hydrogen chloride was complete by evaporation of the ether. The N-(*p*-tolyl)-diphenylacetimino chloride was recrystallized from pentane at −80° and contained 10.8% chlorine (calcd. 11.1%). The melting point was determined by immersing sealed tubes in a melting-point bath at three degree intervals, m.p. 65°.

2-Methyl-4-benzyl-5-oxazolone (V) was prepared according to the procedure of Bergmann[20]; b.p. 87–91° (0.5 mm.), $n^{25}D$ 1.5239.

N-Phenylphthalisoimide was prepared according to the method of van der Meulen,[21] m.p. 114.5–115°.

Reaction of Diphenylketene-*p*-tolylimine (I) with Glacial Acetic Acid.—A mixture of 2.0 g. (7.1 millimoles) of ketenimine I and 6 ml. of glacial acetic acid was swirled at room temperature for 15 minutes. At the end of this time the yellow color was completely discharged and a white precipitate settled to the bottom of the flask. Filtration yielded 1.63 g. (77%) of the amide VII, m.p. 171.5–173.0°. An infrared spectrum of the filtrate was superimposable on that of a solution of acetic anhydride in glacial acetic acid of such concentration as to duplicate that expected from the reaction.

The filtrate was evaporated to dryness *in vacuo* to give an oily residue. Crystallization of the residue yielded 0.33 g. (13%) of the imide III, R = CH_3, m.p. 95–98°.

Treatment of the Imide III (R = CH_3) with Glacial Acetic Acid.—A solution of 0.63 g. (1.83 millimoles) of the imide III (R = CH_3) in 4 ml. of glacial acetic acid was allowed to remain at room temperature for 9 hours. The clear solution was poured onto 125 ml. of ice and water with swirling. The resulting solid amounted to 0.60 g. (96%) and was starting material, m.p. 98–100°.

Reaction of Diphenylketene *p*-Tolylimine (I) with Phthalic and Succinic Acids.—A solution of 0.6 g. (2.12 millimoles) of ketenimine I and 0.36 g. (2.12 millimoles) of phthalic acid in 60 ml. of benzene was refluxed until the yellow ketenimine color was completely discharged. The clear solution was evaporated to dryness *in vacuo* without the application of heat. An infrared spectrum of the white residue showed the characteristic carbonyl doublet of phthalic anhydride at 5.39 and 5.62 μ. Sublimation of the residue at 70° (0.15 mm.) produced 0.28 g. (89%) of phthalic anhydride, m.p. 129–130°. The residue was recrystallized from hexane–acetone to give 0.58 g. (91%) of N-(*p*-tolyl)-diphenylacetamide (VII), m.p. 172–173°.

Following the above procedure, 0.1 g. (47%) of succinic anhydride, m.p. 117.0–118.5°, and 0.36 g. (56%) of the amide, m.p. 172–173°, resulted from the reaction of 0.6 g. (2.12 millimoles) of the ketenimine I and 0.25 g. (2.12 millimoles) of succinic acid.

***p*-Tolylimine (I) with Benzyl Acid Phthalate Followed by Hydrogenolysis.**—Benzyl acid phthalate was prepared according to the method of Walbaum[22] in 63% yield, m.p. 106–108°. A solution of 1.0 g. (3.54 millimoles) of ketenimine I and 0.90 g. (3.54 millimoles) of the ester in 20 ml. of benzene was refluxed until the yellow ketenimine color was discharged completely. The solution was evaporated under reduced pressure and the residue was taken up in 35 ml. of absolute ethanol and hydrogenated at room temperature and atmospheric pressure with a 10% palladium-on-charcoal catalyst (0.3 g.) until 1.3 times the theoretical amount of hydrogen was absorbed. The catalyst was filtered and the clear solution was evaporated to dryness *in vacuo* without the application of heat. An infrared spectrum of the residue showed the characteristic carbonyl doublet of phthalic anhydride at 5.39 and 5.62 μ. The residue was triturated with several portions of warm hexane. From the hexane solution 0.19 g. (36%) of phthalic anhydride was isolated, m.p. 128.0–129.5°, while recrystallization of the residue from hexane–acetone produced 0.61 g. (58%) of the amide, m.p. 168.0–169.5°.

Hydrolysis of the Acetic Acid Adduct III (R = CH_3). To a solution of sodium methoxide (0.0326 mole) in 25 ml. of absolute methanol was added 0.15 g. (0.438 millimole) of the acetic acid adduct. The solution was refluxed for 67 hours and then evaporated to dryness under reduced pressure. The residue was washed well with water, dried, and recrystallized from hexane–acetone. A 61% yield of N-(*p*-tolyl)-diphenylacetamide (VII) resulted, m.p. 172–173°. A mixture melting point with an authentic sample of the amide VII was not depressed, m.p. 172–173°.

Reaction of III (R = CH_3) with *n*-Butylamine.—To a solution of 7.0 g. (20.4 millimoles) of the imide III (R = CH_3) in 60 ml. of tetrahydrofuran was added 1.6 g. (22.0 millimoles) of *n*-butylamine. The solution became warm on admixture and the reaction was heated at reflux for 12 hours. The tetrahydrofuran was evaporated and the resulting solid filtered and washed with petroleum ether. The solid amounted to 5.6 g. (92%) of amide VII, m.p. 167–169°. The petroleum ether was evaporated from the filtrate, which consisted of two layers, and the residual N-butylacetamide[23] purified by distillation to give 1.4 g. (60%), $n^{24}D$ 1.4395.

(20) M. Bergmann, F. Stern and C. Witte, *Ann.*, **449**, 277 (1926).

(21) P. H. van der Meulen, *Rec. trav. chim.*, **15**, 282 (1896).

(22) H. Walbaum, *J. prakt. Chem.*, [2] **68**, 242 (1903).

(23) R. H. Wiley, O. H. Borum and L. L. Bennett, Jr., THIS JOURNAL, **71**, 2899 (1949).

Reaction of N-*p*-Tolyldiphenylacetimide (III, R = $(C_6H_5)_2CH$) **with *p*-Toluidine.**—A solution of 0.4 g. (0.8 millimoles) of the imide III (R = $(C_6H_5)_2CH$) and 0.8 millimole of *p*-toluidine in 15 ml. of toluene was refluxed for 80 hours and then evaporated to dryness *in vacuo*. The resulting white solid, m.p. 169–172°, was recrystallized from 95% ethanol to yield 0.3 g. (61%) of N-(*p*-tolyl)-diphenylacetamide (VII), m.p. 179–180°.

Reaction of Adduct XII with *p*-Toluidine.—A solution of 3.6 g. (20 millimoles) of ethyl-*n*-butylketene *n*-butylimine[7] and 8.5 g. (40 millimoles) of diphenylacetic acid in 60 ml. of dioxane was refluxed for 12 hours and then evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml. of ethyl acetate and washed three times with a saturated sodium bicarbonate solution, two times with water and finally two times with saturated sodium chloride solution. The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness *in vacuo* to yield 6.57 g. (84%) of the oily diphenylacetic acid adduct of the ketenimine XII.

The adduct was dissolved in 50 ml. of dioxane and refluxed for 50 hours with 10.0 g. (0.1 mole) of *p*-toluidine. The clear solution was evaporated to dryness *in vacuo* to yield an oily residue which was dissolved in 150 ml. of ethyl acetate and washed three times with 3 *N* hydrochloric acid, two times with water and finally two times with a saturated solution of sodium chloride. The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness *in vacuo*. Petroleum ether (30–60°) was added to the oily residue and the contents were cooled overnight at 4°. The resulting crystalline solid was collected by filtration and washed with cool petroleum ether to yield 1.35 g. (27% based on the adduct) of N-(*p*-tolyl)-diphenylacetamide, m.p. 167–169°. Recrystallization from hexane–acetone raised the melting point to 172–173° and a mixture melting point with authentic amide was not depressed.

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DETROIT 2, MICHIGAN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE STATE UNIVERSITY]

Nitrogen Analogs of Ketenes. V.[1] Formation of the Peptide Bond

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Nitrogen analogs of ketenes have been used as reagents for the formation of the peptide bond. The N-protected amino acids glycine, alanine and methionine were converted in high yield to stable, crystalline adducts with the ketenimine I. The adducts were formed in non-polar, aqueous or alcoholic solutions. Reaction of an amino acid ester with an adduct afforded the peptides; alternately, the three starting materials could be placed in the reaction mixture at the same time. *p*-Aminobenzoic acid ethyl ester was acylated in good yield. Dipeptide derivatives of L-cysteinyl-L-tyrosine and L-asparaginyl-L-cysteine were prepared in about 30 and 45% yield, respectively, indicating that the phenol of tyrosine need not be protected and that dipeptides of good optical purity could be obtained by this method.

In the previous paper[1] in this series, the nitrogen analogs of ketenes were found to react with carboxylic acids with the formation of imides and these imides were found to be active acylating agents. In view of the striking success of carbodiimines[4] as reagents for the formation of peptides, the purpose of this investigation was to determine the use of the ketenimines for the same purpose.

The reaction of phthaloylglycine (II) with the ketenimine I gave the adduct III in 92% yield. The adduct was purified by recrystallization and was stable. Similar adducts from N-carbobenzoxyglycine, phthaloyl-β-alanine, and phthaloyl-DL-methionine were prepared in 89, 76 and 60% yields, respectively. An inert solvent was satisfactory for the adduct formation, although ethanol–water and dioxane–water reaction mixtures could be used.

Acylation of glycine ethyl ester with the adduct II produced the dipeptide derivative, phthaloylglycylglycine ethyl ester, in 70% yield. In the presence of an appropriate base, amino acid or peptide ester hydrochlorides could be used as the starting materials. The tripeptide derivative, phthaloylglycylglycylglycine ethyl ester, was prepared in 50% yield from the adduct III and glycylglycine ethyl ester hydrochloride in the presence of triethylamine.

Ethyl *p*-aminobenzoate was used to test the ability of the adduct III to acylate an aromatic amine. After reaction in benzene solution the product, ethyl phthaloylglycyl-*p*-aminobenzoate, was isolated in 73% yield. A similar reaction was performed in methylene chloride in which the three starting materials ketenimine I, phthaloylglycine and ethyl *p*-aminobenzoate were placed in the reaction mixture at the same time. The yield of product was 77%. In view of the mechanism of the reaction of ketenimines with carboxylic acids as described in the previous paper,[1] the acylation of the amino acid ester in this latter reaction probably proceeded in part *via* the isoimide adduct.

In each of the reactions described so far, the by-product amide V was separated easily from the peptide derivative by taking advantage of solubility differences in various solvents. In other examples the separation problem was not as easily solved. In these examples the peptide ester was selectively saponified and removed as a carboxylic acid. In the preparation of phthaloylglycyl-L-leucine, the reaction mixture was subjected to acid

(1) Part IV describes the reaction of ketenimines with carboxylic acids and is in THIS JOURNAL, **80**, 4065 (1958).

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(4) J. C. Sheehan and G. P. Hess, THIS JOURNAL, **77**, 1067 (1955), and later papers; L. Velluz, G. Amiard, J. Bartos, B. Goffinet and R. Heymes, *Bull. soc. chim. France*, 1464 (1956).