formyl fluoride (61% of the theoretical over-all yield). Only a minor amount of acetyl fluoride was detected.

Aromatic Aldehydes.—(a) Formyl fluoride (24 g., 0.5 mole) was dissolved in 1.0 mole of the corresponding alkylbenzene (toluene, xylene, mesitylene, isodurene) at −30–70° (depending on the freezing point of the hydrocarbon). Into this cold solution boron trifluoride was introduced to saturation (0.5 mole). Generally a deeply colored complex lower layer is formed. The mixture was then allowed slowly to warm up to room temperature. The complex decomposed with strong boron trifluoride evolution. The reaction mixture was washed acid-free with water, dried over calcium chloride and fractionated.

(b) One-half mole of the corresponding aromatic hydrocarbon was dissolved in 150 ml. of CS_2. While the temperature of the reaction mixture was maintained at 0 to 10° a slow stream of formyl fluoride and boron trifluoride (in the ratio of 1:1) was passed through with stirring. After 3 hours when a weight increase corresponding to the reaction of 0.5 mole of formyl fluoride was observed (in the form of the boron fluoride complex) the interaction was stopped, the reaction mixture was stirred for another half-hour, then washed acid-free with cold water, dried over calcium chloride and fractionated. The following aldehydes were prepared: benzaldehyde (56% yield), tolualdehyde (*p*–*o*-isomer mixture, 75%), dimethylbenzaldehyde (mixture, 78%). 2,4,6-trimethylbenzaldehyde (70%), 2,3,4,6-tetramethylbenzaldehyde (72%), naphthaldehyde (α-with about 20% β, 67%).

Alkyl (Aryl) Formates.—One-half mole of the corresponding alcohol (phenol) and 0.5 mole of tri-ethylamine were dissolved in 150 ml. of dry ether. Into the stirred solution was introduced 24 g. (0.5 mole) of formyl fluoride. The temperature of the reaction mixture was kept around 0°. After the addition of the formyl fluoride was completed the stirring was continued for an additional half-hour. The precipitated amine hydrofluoride was filtered off. The ethereal solution was fractionated. The following formates were prepared: methyl (89% yield), ethyl (92%), *n*-propyl (81%), *n*-butyl (80%), *sec*-butyl (84%), *n*-amyl (78%), isoamyl (79%), *n*-octyl (73%), benzyl (69%) and phenyl (75%).

Alkyl (Aryl) Thiolformates—One-half mole of the corresponding mercaptans (thiophenol) and 0.5 mole of triethylamine was dissolved in 200 ml. of dry ether. Formyl fluoride (24 g., 0.5 mole) was introduced into the stirred solution while maintaining the temperature with ice cooling at 0 to 5°. After the addition of the formyl fluoride was completed the stirring was continued for an hour. The precipitated triethylamine hydrofluoride was filtered off and the ethereal solution was fractionated. Date on the thiolformates obtained are summarized in Table I.

Formamides. (a) **Excess Amine as Acid-binding Agent.**—One mole of the corresponding primary or secondary amine was dissolved in 200 ml. of dry ether and treated with 24 g. (0.5 mole) of formyl fluoride while maintaining the temperature about 0°. After the addition of the formyl fluoride was completed the stirring was continued for an additional half-hour. The precipitated amine hydrofluoride was filtered off and the ethereal solution fractionated. (In the case of N-benzyl formamide the ether was distilled off and the solid residue recrystallized from alcohol.) The following N-alkyl formamides were obtained: N-methyl (89% yield), N,N-dimethyl (92%), N-isopropyl (87%), N,N-dipropyl (90%), N-isobutyl (85%), N,N-di-isobutyl (93%), N,N-di-*n*-butyl (86%), N-octyl (88%), N-allyl (79%), N-morpholine (90%), N-benzyl (87%), N-cyclohexyl (83%), N-β-phenylethyl (85%).

(b) **Triethylamine as Acid-binding Agent.**—One-half mole of the corresponding primary or secondary amine and 50.5 g. (0.5 mole) of triethylamine were dissolved in 200 ml. of dry ether and treated with stirring with 24 g. (0.5 mole) of formyl fluoride while maintaining the temperature about 0°. After the addition of the formyl fluoride was completed the stirring was continued for a half-hour. The precipitated amine hydrofluoride was filtered off and the ethereal solution fractionated.

SARNIA, ONTARIO, CANADA

[CONTRIBUTION FROM THE APPLIED CHEMISTRY DEPARTMENT OF THE INDIAN INSTITUTE OF TECHNOLOGY]

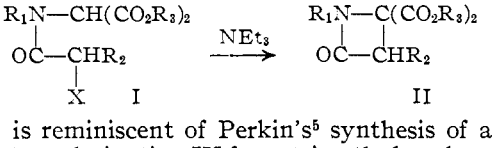
Ease of Cyclization to the β-Lactam Ring[1]

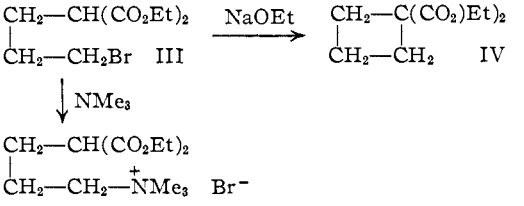
BY AJAY K. BOSE,[2] B. N. GHOSH-MAZUMDAR AND B. G. CHATTERJEE

RECEIVED JUNE 24, 1959

The cyclization of ω-haloacylaminomalonic esters in presence of bases has been studied. Four- and five-membered lactams are formed with ease when triethylamine at room temperature is used, but six- and seven-membered lactams are not obtained under these conditions. Attempts to cyclize the N-chloroacetyl derivatives from benzylaniline, phenylglycine ester and α-anilinophenylacetic ester were unsuccessful. Several 3-substituted azetidin-2-ones were prepared by the cyclization of appropriate malonic ester derivatives. Substituents included chloro, bromo and phthalimidomethyl groups.

The method of Sheehan and Bose[3,4] for the synthesis of β-lactams involving the cyclization of an α-haloacetamidomalonic ester I in the presence of such a weak base as triethylamine at room temperature, is reminiscent of Perkin's[5] synthesis of a cyclobutane derivative IV from trimethylene bromide and diethyl malonate. Walborsky[6] has shown that the cyclization of diethyl ω-bromopropylmalonate (III) takes place in presence of such a strong base as sodium alkoxide. When trimethylamine is used as the base, only the quaternary salt from III is formed. The yield of the cyclization product IV, even in the presence of a strong base, is far from quantitative.





The cyclization of I involves the intramolecular alkylation of an amidomalonic ester instead of an alkylmalonic ester as in Perkin's synthesis. Extensive work has been done on the intermolecular alkylation of acetamidomalonic ester and similar

(1) Presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959. Abstracted from the Ph.D. dissertation of B. N. Ghosh-Mazumdar submitted to the Indian Institute of Technology in 1957.

(2) Chemistry Department, Stevens Institute of Technology, Hoboken, N. J.

(3) J. C. Sheehan and A. K. Bose, THIS JOURNAL, **72**, 5158 (1950).

(4) J. C. Sheehan and A. K. Bose, *ibid.*, **73**, 1261 (1951).

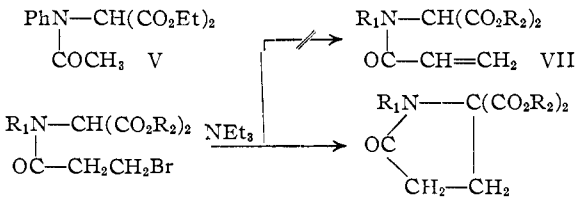
(5) W. H. Perkin, *Ber.*, **16**, 1793 (1883).

(6) H. N. Walborsky, THIS JOURNAL, **71**, 2941 (1949).

amidomalonic esters. Such alkylations have invariably been carried out in the presence of a strong base, such as sodium alkoxide.

The intramolecular alkylation of I is remarkable in that it can be carried out in the presence of a weak base and at room temperature in a high yield. We have tried to alkylate diethyl N-phenylacetamidomalonate (V) with such an active alkylating agent as ethyl bromide in presence of triethylamine but without success.

One difference between I and II is that the halogen in the former is adjacent to a carbonyl group (although an amide carbonyl) and is therefore likely to be more reactive than the alkyl halide type halogen in III. We have, however, found that when V is treated with ethyl bromoacetate and triethylamine, only the quaternary salt from the halo-ester is formed.



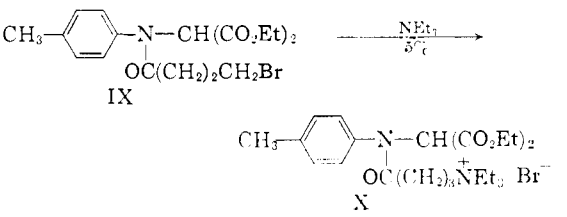
VIa, R_1 = Ph, R_2 = Et
VIb, R_1 = Ph, R_2 = CH_2Ph
VIc, R_1 = *p*-tolyl, R_2 = Et

VIIIa, R_1 = Ph, R_2 = Et
VIIIb, R_1 = Ph, R_2 = CH_2Ph
VIIIc, R_1 = *p*-tolyl, R_2 = Et

To further investigate whether the activation of the halogen by the amide carbonyl plays a significant role, we prepared VIa, VIb and VIc by the reaction of the appropriate aminomalonic ester with β-halopropionic acid and phosphorus trichloride. When these compounds were treated with triethylamine at room temperature, there was an immediate separation of triethylamine hydrohalide in high yield. The halogen-free reaction product could have either of the structures VII and VIII.

Infrared spectra afford an easy way of distinguishing between VII and VIII. In VII the amide carbonyl should absorb at 6 μ or at a higher wave length whereas in VIII the amide carbonyl which is part of a five-membered ring should absorb at a lower wave length. Furthermore, VII should show the characteristic absorptions due to an end methylene group. The infrared spectrum of the halogen-free reaction product from VI had absorption peaks at 5.75 and 5.85 μ. The former is clearly due to the ester carbonyl; the latter is consistent with a γ-lactam structure. The Anglo-American penicillin project reported that fused γ-lactams absorb in the 5.70–5.90 μ range.[7] The characteristic C–H deformation bands of $CH{=}CH_2$ at 10 and 11 μ were absent showing that the acylic structure VII was untenable. The ultraviolet spectrum showed no absorption peak.

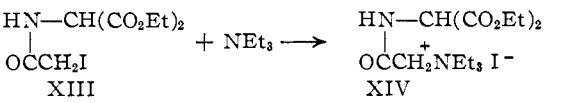
When diethyl (N-4-bromo-*n*-butyryl)-*p*-toluidinomalonate (IX) was treated with triethylamine, no immediate reaction could be seen. After several weeks at room temperature most of the starting material and a small amount of crystals were obtained. The crystalline material, which was a quaternary salt, was assigned the structure X because its infrared spectrum showed a peak at 5.99 μ characteristic of an amide carbonyl. Under the influence of triethylamine the compounds XI and XII also failed to cyclize to the corresponding δ- and ε-lactams.



IX

X

XI, *n* = 2
XII, *n* = 3



XIII XIV

In the carbocyclic series five- and six-membered rings are formed more easily than smaller rings. The extreme ease of formation of four- and five-membered lactam rings is in sharp contrast to the failure to cyclize analogous intermediates to six- and seven-membered lactams. Using molecular models with proportionate atomic radii, it is found that γ-lactam and δ-lactam systems can be made without any great strain being apparent. It is true that the amidomalonic esters under consideration represent many substituents in a small molecule. Nevertheless, the models do not indicate any extra steric factors in IX, XI or XII as compared to I or VI.

In this connection it is interesting to note that when XIII was treated with triethylamine, the quaternary salt XIV was formed and there was no cyclization.[4]

It seems that in general the heavily substituted β-lactams are quite stable. The failure of the N-unsubstituted intermediate XIII to cyclize may be ascribed largely to an enhanced ring strain in an N-unsubstituted β-lactam.

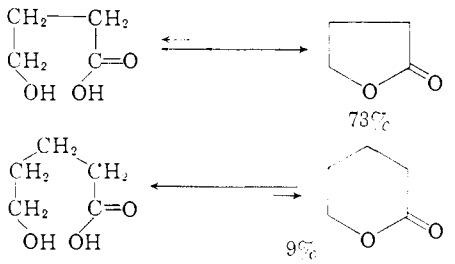
In the case of a six- or seven-membered ring, the strain due to valence angle deviation would not be expected to prevent cyclization—at least not any more than in the case of a five-membered ring. However, this may not be true when one of the ring carbons is part of a carbonyl group. Thus, according to Brown and co-workers,[8] reactions will proceed in such a manner as to favor the formation or retention of an *exo* double bond in a five-membered ring and to avoid the formation or retention of the *exo* double bond in a six-membered ring system. It is known that sugar hemiacetals prefer the six-membered pyranose form to the five-membered furanose form, but aldonic acids prefer the γ-lactone structure to the δ-lactone structure. The equilibrium data in Table I further support this

(7) H. T. Clarke, J. R. Johnson and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, New York, N. Y., 1949, p. 391.

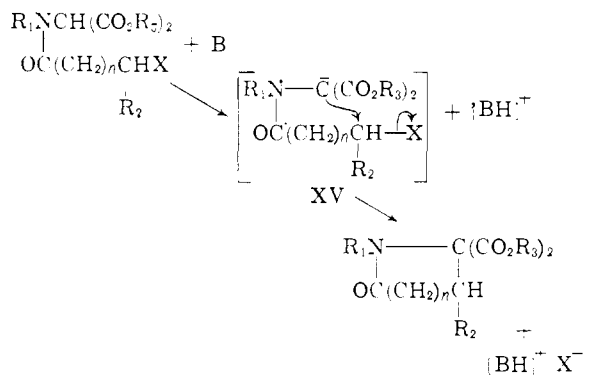
(8) H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954).

view.[9] Since lactams are close analogs of lactones, it may be permissible to extend these considerations to the case of five- and six-membered lactams, too.

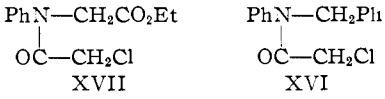
TABLE I



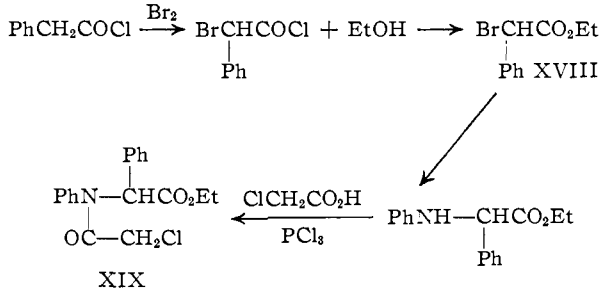
If the formation of the carbanion XV is a prerequisite for the cyclization of I, the rate of intramolecular alkylation will depend on the rate of the carbanion formation and therefore on the activity of the methine hydrogen. With this point in mind we have investigated a few systems where the activating influence is exercised by substituents other than two ester groups as in I.



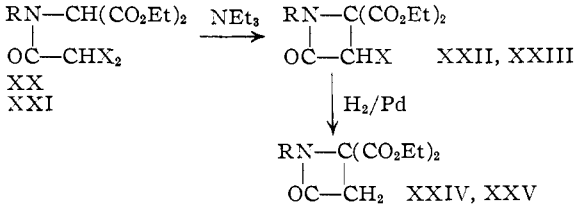
The compounds XVI and XVII prepared by the chloroacetylation of benzylaniline and N-phenylglycine ethyl ester, respectively, failed to cyclize in presence of triethylamine or sodium alkoxide.



Ethyl α-phenylchloroacetanilidoacetate (XIX), prepared from phenylacetyl chloride *via* ethyl α-bromophenylacetate (XVIII), also failed to cyclize to the corresponding β-lactam.

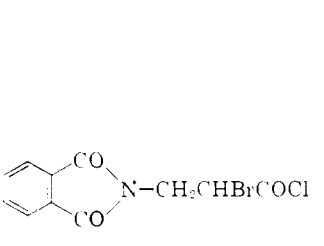


Dihaloacylamidomalonates XX and XXI, obtained readily by the reaction of the corresponding aminomalonate with a dihaloacetic acid in presence of phosphorus trichloride, underwent cyclization on treatment with triethylamine. That the products XXII and XXIII were β-lactams was indicated by their spectrum. The halogen in these β-lactams were unreactive toward silver nitrate and sodium iodide but it was easily removed by catalytic hydrogenation to give the β-lactams XXIV and XXV previously reported by Sheehan and Bose.[3,4]

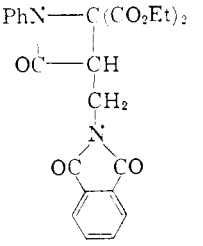


for XX, XXII and XXIV, R = Ph, X = Br
for XXI, XXIII and XXV, R = *p*-tolyl, X = Cl

Triethylamine at room temperature proved to be a suitable base for the cyclization of yet another analog of I. When diethyl anilinomalonate was acylated with β-phthalimido-β-bromopropionyl chloride (XXVI) and the product was treated with triethylamine, separation of triethylamine hydrobromide started almost immediately and the β-lactam XXVII was formed.



XXVI



XXVII

Acknowledgments.—Thanks are due to the Upjohn Company for the analysis of several compounds and to Dr. D. K. Roy Chaudhuri for several of the infrared spectra reported. Thanks are also due to Dr. M. S. Muthana for valuable suggestions and to Dr. S. K. Bhattacharyya and Dr. S. R. Sen Gupta for their interest.

Experimental

Diethyl Acetanilidomalonate (V).—A solution of 10 g. of diethyl anilinomalonate, 4.6 g. of acetic anhydride and a drop of concentrated sulfuric acid in 100 ml. of benzene was heated under reflux for 3 hours. The solvent was then removed under reduced pressure and the residual oil was stirred with an excess of water when the product (8.5 g., 73%) solidified and was collected by filtration. An analytical sample, m.p. 57–58°, was prepared by crystallization from ligroin.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48; N, 4.77. Found: C, 61.28; H, 6.68; N, 4.73.

Attempted Alkylation of Diethyl Acetanilidomalonate (V).—A solution of 0.5 g. of V in benzene was treated with 0.15 ml. of ethyl bromide and 0.25 ml. of triethylamine. After 4 days only a few crystals had formed which were removed by filtration. The filtrate was washed with dilute hydrochloric acid and with water, dried over sodium sulfate and evaporated when the starting material was recovered.

To a benzene solution of 1 g. of V were added 0.4 ml. of ethyl bromoacetate and 0.5 ml. of triethylamine. After 5 minutes the reaction mixture became turbid and after 1.5 hours a quantity of crystals had formed. The crystals were removed by filtration and the filtrate was washed, dried

(9) J. Mathieu and A. Allais, "Principes de Synthese Organique," Masson et Cie, Paris, 1957, p. 428.

and evaporated when the starting material V was recovered. The crystalline product was a quaternary ammonium salt with the bromoacetic ester because no free base could be extracted with ether or benzene after an aqueous solution of the crystals had been made alkaline.[10]

The same crystalline product was obtained when triethylamine was added to a benzene solution of ethyl bromoacetate.

1-Phenyl-5,5-dicarbethoxy-pyrrolidin-2-one (VIIIa).—A solution of diethyl anilinomalonate (5 g.) in benzene (40 ml.) was heated under reflux with β-bromopropionic acid (3.1 g.) and phosphorus trichloride (1.5 ml.) for 2 hours. After removing the solvent under reduced pressure, the residue was agitated with water when a brown oil (8 g.) was obtained. This oil was dissolved in ether, washed with sodium bicarbonate solution, dried and evaporated to give the desired diethyl β-bromopropionanilidomalonate (VI).

To a benzene solution of 5 g. of this compound was added 2 ml. of triethylamine when the reaction mixture warmed up and separation of triethylamine hydrobromide started immediately. After a few hours this crystalline material (1.9 g., 82%) was filtered off and the filtrate was washed, dried and evaporated to give 4 g. of a brown liquid which was distilled under vacuum to afford 2.1 g. (53%) of a yellow, viscous oil which was halogen-free. The infrared spectrum had peaks at 5.67 and 5.85 μ. Distillation of the γ-lactam failed to give an analytically pure sample, but the molar refraction was satisfactory: $n^{25}D$ 1.5136, d_{30} 1.7586; *MR* calcd. 78.11, *MR* found 78.88.

1-Phenyl-5,5-dicarbobenzyloxy-pyrrolidin-2-one (VIIIb).—Using the same method as in the previous experiment, 3 g. of dibenzyl anilinomalonate, 1.3 g. of β-bromopropionic acid and 0.26 ml. of phosphorus trichloride were allowed to react to give 4 g. of the acylated product which was purified by evaporative distillation. When a benzene solution of 3 g. of this intermediate was treated with triethylamine, there was an immediate formation of crystalline triethylamine hydrobromide. On working up the reaction mixture in the usual manner, 2 g. (80%) of the desired γ-lactam was obtained. An analytical sample, m.p. 95.5–96.5° obtained by recrystallization from ligroin, showed infrared absorption peaks at 5.75 (ester carbonyl) and 5.85 μ (lactam carbonyl).

Anal. Calcd. for $C_{26}H_{23}NO_5$: C, 72.72; H, 5.36; N, 3.26. Found: C, 72.62; H, 5.75; N, 3.31.

1-(*p*-Tolyl)-5,5-dicarbethoxypyrrolidin-2-one (VIIIc).—Using the method described before diethyl N-*p*-tolyl-β-bromopropionamidomalonate, m.p. 65–67°, was obtained in 76% yield from diethyl *p*-toluidinomalonate. Treatment with triethylamine gave the desired γ-lactam in 77% yield as a colorless, viscous liquid that had infrared absorption peaks at 5.75 and 5.85 μ.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.59; N, 4.38. Found: C, 64.12; H, 6.69; N, 4.45.

Diethyl (N-4-Bromo-*n*-butyryl)-*p*-toluidinomalonate (IX).—Using the same general procedure described before, 2.65 g. of diethyl *p*-toluidinomalonate, 1.8 g. of 4-bromo-*n*-butyric acid (prepared from butyrolactone and hydrobromic acid following the method of Henry[11]) and 1 ml. of phosphorus trichloride were allowed to react to give 3.5 g. (82.5%) of a light yellow, viscous oil which showed the absence of N–H stretching bands in the 3 μ region and the presence of strong peaks at 5.75 (ester carbonyl) and 6.0 μ (amide carbonyl). Distillation (120° (0.05 mm.)) did not produce an analytically pure sample.

Anal. Calcd. for $C_{18}H_{24}BrNO_5$: C, 52.30; H, 5.84; N, 3.38. Found: C, 53.51; H, 6.12; N, 3.66.

When a benzene solution of 2.2 g. of the acylated compound was treated with 3 ml. of triethylamine, there was no immediate separation of triethylamine hydrobromide. After a few days a small amount of flaky crystals separated. At the end of seven weeks the reaction mixture was filtered and 0.95 g. of a colorless crystalline material was collected. The filtrate was washed with dilute hydrochloric acid to remove excess triethylamine. After drying, the solvent was removed under reduced pressure when a viscous oil (1.57 g.) was obtained which was identified as the starting material on the basis of its infrared spectrum. The crystalline material showed strong peaks at 5.75 (ester carbonyl) and 5.99 μ (amide carbonyl) and medium peaks between 3.5–4 μ (characteristic of ammonium halide type structure).

Diethyl (N-4-Bromo-*n*-butyryl)-anilinomalonate (XI).—The reaction of 1 g. of diethyl malonate with 0.85 g. of 4-bromo-*n*-butyric acid and 0.3 ml. of phosphorus trichloride gave 1.5 g. (93.5%) of a colorless oil, with λ_{max} 5.70, 5.74 (ester CO), 5.98 μ (amide CO). A sample purified by distillation (120° (0.05 mm.)) had $n^{25}D$ 1.5140.

Anal. Calcd. for $C_{17}H_{25}BrNO_5$: C, 51.04; H, 5.55; Br, 19.98. Found: C, 51.82; H, 5.44; Br, 19.78.

When a benzene solution of this acylated product was treated with triethylamine, only a few crystals of a solid separated after 2 weeks.

Diethyl (N-5-bromo-*n*-valeryl)-anilinomalonate (XII) was obtained in 90% yield from diethyl anilinomalonate, 5-bromovaleric acid (prepared by the hydrolysis of 5-bromovaleronitrile with hydrobromic acid) and phosphorus trichloride. The infrared spectrum (λ_{max} 5.70, 5.75, 6.0 μ) was satisfactory.

When a benzene solution of this acylated product was treated with triethylamine, no perceptible reaction occurred over a period of 7 days.

Ethyl Chloroacetanilidoacetate (XVI).—A solution of 4 g. of N-phenylglycine ethyl ester (prepared from 16.7 g. of ethyl bromoacetate and 18.4 g. of aniline) was heated under reflux for 5 hours with 2.1 g. of chloroacetic acid and 0.63 ml. of phosphorus trichloride. On working up the reaction mixture in the usual manner the acylated product (4 g., 71%) was obtained as a brown liquid. A benzene solution of this compound was treated with triethylamine, but no solid separated in the course of one week. The substitution of sodium ethoxide for triethylamine failed to give any halogen-free, identifiable product.

N-Benzyl Chloroacetanilide (XVII).—Benzylaniline (5 g.), chloroacetic acid (2.6 g.) and phosphorus trichloride (0.8 ml.) were allowed to react in refluxing benzene solution to give about 4 g. of N-benzylchloroacetanilide, m.p. 75° (lit.[12] m.p. 80–81°), λ_{max} 6 μ. The amide was recovered unchanged after treatment with triethylamine or sodium ethoxide.

Ethyl α-Phenylchloroacetanilidoacetate (XIX).—α-Bromophenylacetyl chloride prepared by treating phenylacetyl chloride with bromine in carbon tetrachloride at 80°, was treated with ethyl alcohol to give α-bromophenylacetate. A benzene solution of 5 g. of this ester and 3.8 g. of aniline reacted immediately with the separation of aniline hydrobromide (2.5 g., 66%). On working up the reaction mixture in the usual manner, 5.5 g. of a dark brown liquid was obtained. Without further purification, 4 g. of this liquid was allowed to react with 1.48 g. of chloroacetic acid and 0.45 ml. of phosphorus trichloride in benzene solution to afford 4 g. (77%) of ethyl α-chloroacetanilidophenylacetate, m.p. 92.5° (from ligroin).

Anal. Calcd. for $C_{18}H_{17}ClNO_3$: C, 65.16; H, 5.43; N, 4.22. Found: C, 64.90; H, 5.61; N, 4.36.

A benzene solution of 4 g. of the above compound was treated with triethylamine. After 2 days 0.3 g. of a crystalline precipitate was filtered off and the filtrate washed with dilute hydrochloric acid and with water, dried and evaporated. The residue crystallized on standing and was identified as unchanging starting material (3.5 g.) from its analysis, m.p. and m.m.p.

Anal. Calcd. for $C_{18}H_{17}ClNO_3$: C, 65.16; H, 5.43; N, 4.22. Found: C, 64.83; H, 5.50; N, 4.40.

1-Phenyl-3-phthalimidomethyl-4,4-dicarbethoxy-azetidin-2-one (XXVII).—A benzene solution of 2.5 g. of diethyl anilinomalonate and 3 g. of β-phthalimido-α-bromopropionyl chloride[13] was heated under reflux for 3.5 hours. Hydrogen chloride was evolved during this period. The reaction mixture was washed with water and dilute sodium bicarbonate solution, dried and evaporated when a viscous residue was left that did not crystallize.

On the addition of triethylamine to a benzene solution of this intermediate there was an immediate separation of crystalline triethylamine hydrobromide. After allowing the reaction mixture to stay overnight at room temperature, water was added and the benzene layer separated. The benzene solution was washed, dried and evaporated to give the desired β-lactam in 50% yield (based on diethyl anilino-

(10) P. A. Diassi, THIS JOURNAL, **77**, 4688 (1955).

(11) L. Henry, *Compt. rend.*, **102**, 369 (1886).

(12) Fredrichs, *Arch. Pharm.*, **241**, 218 (1903).

(13) S. Gabriel, *Ber.*, **38**, 630 (1905).

malonate). An analytical sample prepared by recrystallization from ethanol had m.p. 154–155° and a broad infrared absorption peak at 5.60–5.81 μ.

Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 64.00; H, 4.88; N, 6.22. Found: C, 64.41; H, 5.16; N, 5.96.

1-*p*-Tolyl-3-chloro-4,4-dicarbethoxy-azetidin-2-one (XXIII).—A benzene solution of 5.3 g. of diethyl *p*-toluidinomalonate and 3.5 g. of dichloroacetyl chloride was heated under reflux for 3.5 hours. On working up the reaction mixture in the usual manner, 6.45 g. (86.5%) of a yellow, viscous oil was obtained which had peaks at 5.65–5.75 and 5.9 but no absorption at the 3 μ region.

When triethylamine was added to a benzene solution of the above intermediate there was no immediate reaction. After a few days a small quantity of crystals appeared. At the end of several weeks 0.9 g. of crystalline solid was removed by filtration and the filtrate was washed with dilute acid and with water, dried and evaporated. The product (1.46 g., 62%) was a yellow, viscous oil, $n^{25}D$ 1.5277, which showed strong absorption at 5.60 (β-lactam carbonyl) and 5.73 μ (ester carbonyl). Since this compound could not be induced to crystallize, purification was attempted through distillation (110° (0.05 mm.)). The distillate was a light yellow, viscous oil with the following analysis.

Anal. Calcd. for $C_{16}H_{18}ClNO_5$: C, 56.56; H, 5.34; N, 4.12. Found: C, 57.33; H, 5.99; N, 4.25.

No precipitate was formed when this compound was boiled with alcoholic silver nitrate for 15 minutes.

Hydrogenation of 1-(*p*-Tolyl)-3-chloro-4,4-dicarbethoxy-azetidin-2-one.—A solution of 0.5 g. of the halo-β-lactam in ethyl acetate was hydrogenated in presence of 0.3 g. of 10% Pd-on-charcoal and 0.3 g. of magnesium oxide. When the hydrogen uptake stopped, the reaction mixture was filtered and the filtrate evaporated to afford 0.3 g. of crystalline material of m.p. 85–87°. On recrystallization from cyclohexane, the m.p. rose to 89.5–90.5°. It was identified as 1-*p*-tolyl-4,4-dicarbethoxy-azetidin-2-one (XXV) from its m.p., infrared spectrum and m.m.p. with an authentic sample of this β-lactam.

Diethyl dibromoacetanilidomalonate, m.p. 84–85°, λ_{max} 5.75 and 6.0 μ, was prepared in 79% yield by refluxing for 4 hours a benzene solution of diethyl anilinomalonate, dibromoacetic acid and phosphorus trichloride.

Anal. Calcd. for $C_{15}H_{17}Br_2NO_5$: C, 39.91; H, 3.77; N, 3.10. Found: C, 40.31; H, 4.01; N, 3.25.

1-Phenyl-3-bromo-4,4-dicarbethoxy-azetidin-2-one (XXII).—When triethylamine was added to a benzene solution of the above intermediate, an immediate reaction ensued and crystalline triethylamine hydrobromide started to separate. After storing overnight at room temperature the crystals (2.4 g., 98%) were removed by filtration and the filtrate worked up in the usual manner to give a viscous liquid which on evaporative distillation afforded a light yellow colored liquid, $n^{26}D$ 1.5215, λ_{max} 5.68 and 5.74 μ. The liquid could not be obtained analytically pure. However, on catalytic hydrogenation it absorbed nearly one mole of hydrogen and gave the known 1-phenyl-4,4-dicarbethoxy-azetidin-2-one (**XXIV**) in a nearly quantitative yield.

KHARAGPUR, INDIA

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

A Low Pressure Process for the Reduction of Nitriles. Use of Rhodium Catalyst[1]

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A low pressure catalytic reduction procedure for the conversion of sixteen aliphatic nitriles to primary amines is described. The hydrogenations are carried out at room temperature in the presence of ammonia in a Parr apparatus, using 5% rhodium-on-alumina. No hydrogenolysis of the benzyl grouping was observed using this catalyst. Of particular interest is the reduction of 3-indoleacetonitrile to tryptamine under low pressure conditions. Except for 3-indoleacetonitrile the nitrile used in this study are of the type $R(CH_2)_nCN$ wherein R is a substituted nitrogen atom or an ether moiety.

Catalytic hydrogenation of basic nitriles has generally been carried out with nickel using the procedure of Whitmore.[2]

We now find that with rhodium catalyst such drastic conditions are not necessary. As an example of the Whitmore method, in the reduction of 3-indoleacetonitrile Thesing and Schülde[3] used at least an equal weight of Raney nickel catalyst and hydrogen pressure of 90 atmospheres in the presence of ammonia to obtain a good yield of tryptamine.[4a,b,c]

In contrast with these described procedures, low pressure hydrogenation of 3-indoleacetonitrile using a 10–20% ratio of 5% rhodium-on-alumina, in the presence of ammonia, was complete in a short time and a good yield of tryptamine was obtained. However, reduction in the absence of ammonia gave predominantly secondary amine contaminated with some tryptamine. The use of strong base in the absence of ammonia[5a,b] also gave the same result.

The procedure of using rhodium catalyst in the reduction of nitriles has several advantages. There are reports of Raney nickel reduction of basically substituted nitriles under moderate conditions.[6a,b] However, the ease with which they are reduced with rhodium at room temperature and 2–3 atmospheres (in less than two hours) makes this method appear to be the one of choice. In general, yields, as shown in Table I, are good. The method gave good results when applied to the reduction of β-cyanoethyl ethers and should supplant the pro-

(1) Presented at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 14, 1959.

(2) F. C. Whitmore, *et al.*, THIS JOURNAL, **66**, 725 (1944). The method comprises hydrogenation of nitriles with Raney nickel and ammonia at 90–130° and 70–270 atmospheres pressure.

(3) J. Thesing and F. Schülde, *Ber.*, **85**, 324 (1952).

(4) (a) Protiva, *et al.*, *Collection Czech. Chem. Comms.*, **24**, 74 (1959), commented on the large amount of catalyst necessary to achieve a fair yield of tryptamine by this method; (b) W. Schindler, *Helv. Chim. Acta*, **40**, 2156 (1957), prepared isotryptamine from 2-indoleacetonitrile in a similar manner; (c) in this Laboratory erratic results were obtained following the Thesing and Schülde procedure. In some instances as much as 28 hours was required to complete uptake of hydrogen. Hydrogenation was satisfactory only when 200 to 300% by weight of Raney nickel was used.

(5) (a) M. Fluchaire and F. Chambret, *Bull. soc. chim. France*, **11**, 22 (1944); (b) M. Grunfeld, U. S. Patent 2,449,036.

(6) (a) Good yields of some dialkylaminopropylamines are reported by J. H. Burckhalter, E. M. Jones, W. F. Holcomb and L. A. Sweet, THIS JOURNAL, **65**, 2012 (1943), from reduction of the corresponding nitriles with Raney nickel and ammonia at 70° and 4 atmospheres; (b) W. Huber, *ibid.*, **66**, 876 (1944), reduced some basically substituted nitriles in a similar manner at 12 atmospheres in a specially prepared piece of apparatus.