

The Synthesis of Methyl Benzylpenicillanate*

By

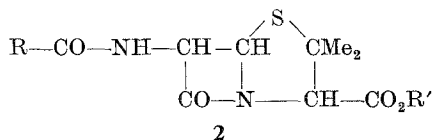
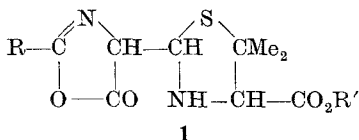
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(Received April 7, 1967)

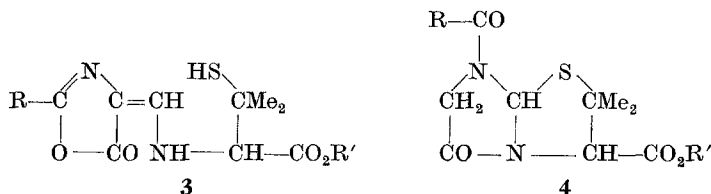
Methyl phenylpenicillanate (**10**) was formed by the interaction of 4-carbomethoxy-5,5-dimethyl- Δ 2-thiazoline (**6**) and 2-phenyl-oxazol-5-one in pyridine, whereas in neutral solvents the preponderant product of the reaction was methyl phenylpenicillanate (**7**). Similarly, under the latter conditions, 2-benzylloxazol-5-one (**5**) and the thiazoline (**6**) yield methyl benzylpenicillanate (**4**, R = Ph · CH₂, R' = Me) identical with the product obtained from the methyl ester of benzylpenicillin.

After the structure of the R-penicilloic acids had been established, the R-penicillins were recognised as their anhydrides and the possibilities were the oxazolone-thiazolidine (**1**) and the β -lactam (**2**). At first the X-ray diffraction evidence appeared to confirm **1**, but as closer approximations were made, the evidence became conclusive in favour of **2** (R = Ph · CH₂; R', monovalent metal)¹.



* This contribution by A. B. A. Jansen and Robert Robinson is dedicated to Professor F. Wessely on the occasion of his 70th Birthday in admiration of his eminent services to chemistry as a teacher and original investigator.

¹ 'The Chemistry of Penicillin' edited by H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton Univ. Press, 1949 (later referred to as C. P.); especially Chapters I, II, and XII; cf. R. Robinson, Early History of the Chemistry of Penicillin, Ramsden Memorial Lecture, Manchester Lit. and Phil. Soc., Memoirs, 1950, Vol. 92.

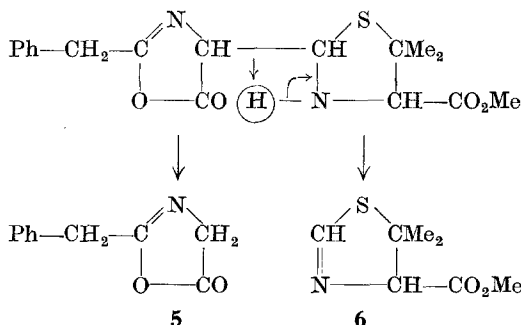


One of us commented² on the close structural relation of 1 and 2, interconversion of which is brought about by a simple hydrogen (proton) transfer.

There is also a close relation between 1 and 3 which represents the structure of the R-penicillenic acids or derivatives (e.g. R = PhCH₂, R' = H or Me). This is exemplified by the ready formation of 3 from R-penicillins by means of mercuric salts under very mild conditions. This could be 2 → 1 → 3 and the reverse process, 3 → 1 → 2 probably occurs in the synthesis of penicillin from penicillenate³.

Methyl benzylpenicillenate (4, R = Ph · CH₂, R' = Me) was obtained⁴ by heating the methyl ester of benzylpenicillin alone under vacuum sublimation conditions (yield about 50%) or in toluene (or aromatic solvent of higher b.p.) in presence of a trace of iodine. By following the changes of rotatory power and UV absorption during this process the formation of methyl benzylpenicillenate as an intermediate was indicated.

It occurred to one of us that 1 was probably another intermediate, the sequence being 2 → 1 ⇌ 3, as indeed is probable in the formation of penicillenate. The component 1 of the equilibrium mixture 1, 3 could suffer fission into 5 and 6, which might recombine to 4. This fission is illustrated by the annexed expression:



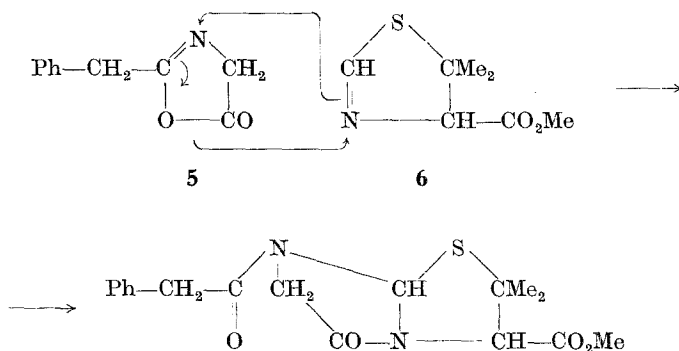
² J. R. Johnson, R. B. Woodward, and R. Robinson, *C. P.*, p. 440 et seq.

³ V. du Vigneaud, J. L. Wood and M. E. Wright, *C. P.*, 892; V. du Vigneaud, F. H. Carpenter, R. W. Holley, A. H. Livermore, and J. R. Rachele, *C. P.*, 1025.

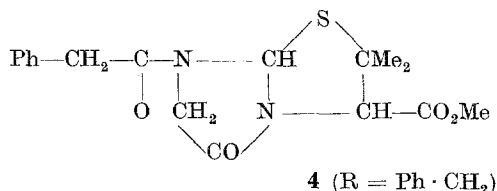
⁴ It should be noted that the term benzylpenicillin (and similar expressions) was not used in accordance with the strict conventions of nomenclature

So far all is in accord with clear analogy but the recombination of **5** and **6** with formation of **4** has no very close precedent. This is, however, a matter of no importance, since it was found to occur with great ease in practice.

5⁵ and **6**⁶ were made by the known methods and afforded **4** when heated together in benzene solution and, less satisfactorily, under other conditions⁷. The reaction may be represented as follows:



which, when re-arranged, is **4**.



based on substitutions. It conforms to these rules if penicillin is taken to be 6-formylaminopenicillanic acid. The penillonnates were discovered by the Merck Group of investigators (Rahway, N. J., U.S.A.) headed by Dr. *K. Folkers*. The reference is to *C. P.*, pp. 158 and 188 et seq.

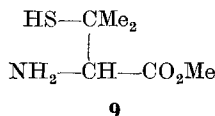
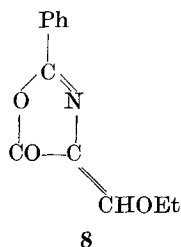
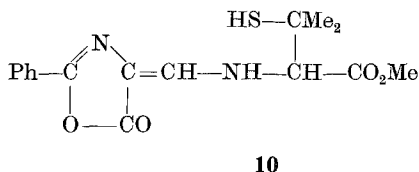
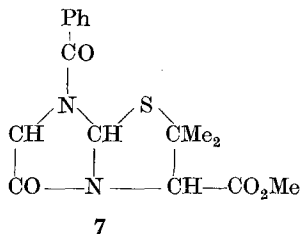
⁵ Merck Report No. 63 (1945). Cf. *C. P.*, pp. 1056—1059 for a list of Reports from Merck & Co. Inc.

⁶ Upjohn Report, U 13a. Cf. *C. P.*, p. 781 described the preparation of this benzyloxazolone. The method given in our text was apparently novel.

⁷ Our main result was mentioned in a footnote, *C. P.*, p. 160. It is also stated therein that the fission-recombination mechanism for the formation of methyl benzylpenillonnate from benzylpenicillin methyl ester was foreshadowed by *R. B. Woodward* in a letter to *K. Folkers* of Jan. 3rd 1945. This suggestion was made on theoretical grounds. The reaction between 2-benzyl-5(4) oxazolone and the methyl ester of D-5,5-dimethyl-Δ²-4-thiazolinecarboxylic acid in toluene at 100° (or 60—70°) was also studied by *W. E. Bachmann* and *M. W. Cronyn* (*C. P.*, p. 877). Methyl benzylpenillonnate was expected and looked for, but not found among the products.

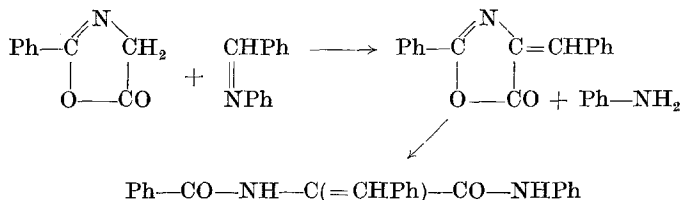
Essentially the transformation is the acylation of the thiazoline nitrogen by the reactive carbonyl of the oxazolone.

Methyl phenylpenillonate (7)⁸ has also been synthesized by reaction of the thiazoline ester (6) with 2-phenyloxazolone⁹. In this case an alternative method was realised, namely the condensation of 2-phenyl-4-ethoxymethyleneoxazolone (8) with *d*-penicillamine methylester (9). The intermediate in this case is obviously methyl phenylpenicillenate (10).



The later stages will be analogous to those described above for the benzyl analogue.

N-benzylidene-aniline and 2-phenyloxazolone reacted in pyridine solution to form 2-benzamidocinnamic anilide, a reaction that can be represented as follows:



A similar reaction between benzyloxazolone and N-benzylideneaniline has been examined by *C. W. Bird*¹⁰ who identified as products the 2-

⁸ Merck Report, No. 12a.

⁹ *C. P.*, pp. 171 (Abbott, A, 6a, 1), 713, 730, 778, 781, 915.

¹⁰ *C. W. Bird*, Tetrahedron Letters, 1964, 609. The interesting rearrangement of a substituted β -lactam described in this paper is certainly analogous

benzylidene derivative of the oxazolone and N-phenylacetyl-glycine anilide. This author does not approve our idea of fission and recombination presumably because, as he says, the latter is without precedent. As already stated, this is irrelevant to the explanation of a reaction that can be shown to happen and in any case the analogies mentioned above appear to be adequate.

This work was carried out in 1945 and 1946 and described in a D. Phil. Thesis (A. B. A. Jansen, Oxford, of 1947).

Experimental

Absorption spectra were determined in methanolic solution. Light petroleum, b.p. 80–90°, is termed ligroin. M. pts. are uncorrected.

Reaction of 4-Carbomethoxy,5,5-dimethylthiazoline with 2-Phenyl-oxazolone

The d-thiazoline ester was prepared according to the known procedure. A specimen was converted to the *Reineckate* by solution in dilute hydrochloric acid and addition of a saturated aqueous solution of Reinecke's salt, when a violet precipitate, m.p. 160°, was obtained (Found in material dried at 100° in vacuo: C, 27.0; H, 3.8; Cr₂O₃, 15.6. [C₇H₁₂O₂NS]⁺ [Cr(NH₃)₂(CNS)₄]⁻ requires C, 26.8; H, 3.7; Cr₂O₃, 15.5%). This derivative proved useful for the identification of the thiazoline, especially when the latter occurred in mixtures.

(a) *In Pyridine.* 2-Phenyl-oxazolone (0.54 g.) and the thiazoline ester (0.58 g.; 1 mol.) were dissolved in dry pyridine (5 c.c.) and, after 2½ hours at room temperature, the mixture was poured on to ice and dilute hydrochloric acid. The gum, which separated, was collected in ether, washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, then dried and the solvent evaporated. The residual resin (1 g.) was refluxed repeatedly with portions of ligroin, the extracts decanted, cooled rapidly and centrifuged till clear. On keeping for several hours these extracts deposited colourless prisms (0.47 g.), m.p. 110–130°. To effect purification the crystals were dissolved in ether (50 c.c.) and an excess of an ethereal solution of mercuric chloride was added. The precipitate was washed several times with ether by decantation, and was then suspended in ether (50 c.c.) and 0.2 N phosphate buffer solution (25 c.c., pH 7) then added. The mixture was saturated with hydrogen sulphide, the ethereal layer separated, dried and evaporated. The residue crystallized from isopropyl ether, yielding colourless prisms (0.35 g.), m.p. 110–130° (Found: C, 57.5; H, 5.4; N, 8.15; S, 9.6. Calc. for C₁₆H₁₈O₄N₂S: C, 57.5; H, 5.4; N, 8.4; S, 9.4%). The substance gave a positive reaction with

to the penicillin ester to penicillinate change and occurs under similar conditions. The simpler case and the penicillin case are parallel and so far as the rearrangement is concerned clearly are in the same category. The only real difference between our hypothesis and that of *Bird* is that we assume a break of the amide link of the β-lactam whereas he keeps this intact during the process. Further work is needed before the question so arising can be answered. Meanwhile N-benzylideneaniline is *not* quite analogous to the thiazoline ester; its electrophilic reactivity at the methine group is much the greater and hence the formation of a benzylidene derivative is to be expected.

the iodine-azide reagent but no colouration with sodium nitroprusside or ferric chloride solutions. It showed absorption maxima at 2,400 Å (ϵ , 11,060) and at 3480 Å (ϵ , 28,700). (The methyl phenylpenicillenate prepared by the Merck group¹¹ had absorption maxima at 2400 Å (ϵ , 12,000) and at 3500 Å (ϵ , 34,000).

A portion of the product was dissolved in ether and a few drops of benzylamine added. In the course of an hour a solid had separated with was collected and crystallized from methanol, giving colourless needles, m. p. 204—206° (Found: C, 62.5; H, 6.25; N, 9.2; S, 7.2. Calc. for $C_{23}H_{27}O_4N_3S$: C, 62.5; H, 6.15; N, 9.5; S, 7.3%).

The material not dissolved by ligroin (0.3 g.) remaining after the extraction of the original resin was dissolved in ether and treated with an excess of ethereal mercuric chloride. A negligible quantity of substance remained in solution after separation of the precipitate. The latter, decomposed with hydrogen sulphide as described above, yielded a gum which could not be crystallized but gave a small amount (0.1 g.) of the benzylamide, m.p. 204 to 206°, on treatment with benzylamine in ether.

(b) *In Ether*. A solution of the thiazoline ester (2.6 g.) and 2-phenyl-oxazolone (2.4 g., 1 mol.) in dry ether (50 c.c.) was refluxed for 3 hours when a test portion no longer afforded any thiazoline Reineckate. The liquid was decanted from some insoluble resin which had formed and the latter was extracted twice with boiling ether. The combined ethereal solutions were washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, and then dried and evaporated, leaving a gum (4.2 g.); absorption maxima at < 2200 Å (ϵ , > 10,300) and at 3510 Å (ϵ , 4,600). An excess of ethereal mercuric chloride solution was added to this product, redissolved in ether (100 c.c.), and the resulting precipitate was collected, washed with ether and decomposed as above, yielding a resin (1.6 g.). This could not be crystallized but gave the crystalline benzylamide, m.p. 204—206°, on treatment with benzylamine in ether.

The ethereal filtrate and washings were freed from mercuric chloride by treatment with hydrogen sulphide in the presence of phosphate buffer and the dried solution was evaporated, leaving a pale yellow oil (2 g.) which partially crystallized. Recrystallization of this product from ethanol (2 c.c.) gave colourless needles (1.5 g.), m.p. 120—121°, of *methyl phenylpenicillanate* (Found: C, 57.5; H, 5.55; N, 8.65; S, 9.5. $C_{16}H_{18}O_4N_2S$ requires C, 57.5; H, 5.4; N, 8.4; S, 9.4%). (This compound was first isolated from the crude reaction mixture by extraction with hot ligroin but the above procedure is much to be preferred). The substance gave no reaction with the iodine-azide reagent and was recovered unchanged after boiling with water for 3 hours and after heating at 100° with benzylamine in benzene for 6 hours.

Methyl Phenylpenicillanate (7)

d-Penicillamine methyl ester hydrochloride (0.5 g.) and 2-phenyl-4-ethoxy-methylene-oxazolone (0.5 g.) (C.P.) were dissolved in pyridine (5 c.c.) and, after 15 hours at room temperature, the mixture was added to ice and dilute hydrochloric acid. The product was collected in ether, washed with dilute acid, dried, and treated with an excess of ethereal mercuric chloride solution. The precipitate was washed with ether and decomposed with hydrogen sulphide in the usual manner to yield a gum from which prisms (0.1 g.) were obtained by extraction with ligroin. These had m.p. 110—130°, unchanged

¹¹ Merck Report, 20a.

by recrystallization from isopropyl ether and not depressed on admixture with the product prepared as above from 4-carbomethoxy-5,5-dimethylthiazoline. Addition of benzylamine to an ethereal solution of the compound gave the benzylamide, m.p. and mixed m.p. 204—206°.

Hydrolysis of Methyl Phenylpenicillinate

A suspension of the compound (0.1 g.) in 2 N hydrochloric acid (1 c.c.) was heated in a sealed tube in a steam bath for 2 hours. The mixture was then cooled and centrifuged, and the clear supernatant aqueous solution was pipetted from the yellow oil (50 mg.). The latter crystallized from ligroin to give the unchanged substrate. The aqueous solution was distilled until about one third of its volume had been collected as distillate. This contained no formaldehyde but gave a positive test for formic acid by the method of *Frehdén* and *Fürst*¹². The residual solution deposited crystals (10 mg.) which were collected and recrystallized from water, m.p. 187°, not depressed on admixture with hippuric acid. The filtrate, which was made just acid to litmus, gave the deep blue colouration characteristic of penicillamine on the addition of aqueous ferric chloride solution.

As a control the experiment was repeated using a mixture of penicillamine methyl ester and hippuric acid; no formic acid was produced in this case.

Methyl Phenyldesthiopenicillinate

Methyl phenylpenicillinate (0.2 g.) in methanol (10 c.c.) was refluxed with Raney nickel (1 c.c. of sediment) for 3 hours. The solution was filtered from the nickel and evaporated under reduced pressure, leaving a gum (0.18 g.) which crystallized from ligroin in colourless needles (0.15 g), m.p. 118—119° (Found: C, 62.9; H, 6.7; N, 9.1. $C_{16}H_{20}O_4N_2$ requires C, 63.2; H, 6.6; N, 9.2%).

Hydrolysis of Methyl Phenyldesthiopenicillinate

The desthio compound (0.4 g.) was heated in a sealed tube with 2 N hydrochloric acid (6 c.c.) for 2½ hours at 100° when a clear solution was obtained. After 24 hours in a refrigerator this had deposited a crystalline product which was collected and digested with ether. The ether insoluble portion (20 mg.) was recrystallized from water giving colourless prisms of an *acid*, m.p. 201—203° Found: C, 62.05; H, 5.9. $C_{15}H_{18}O_4N_2$ requires C, 62.1; H, 6.2%). Evaporation of the ethereal extract gave benzoic acid (0.1 g.), m.p. and mixed m.p. 121°. Part of the aqueous filtrate was made very weakly acid and dimedone solution added. The precipitate of methylene-bisdimedone was collected and crystallized from aqueous alcohol. It had m.p. 187°, not depressed on admixture with an authentic specimen. Concentration of the remainder of the filtrate gave a further crop of crystals which were separated by means of ether affording benzoic acid, and hippuric acid, m.p. and mixed m.p. 187°.

*2-Benzylidenepseudoxazalone*¹³

Phenylbromacetyl glycine (12 g.)¹⁴ was added to a mixture of acetic anhydride (100 c.c.) and pyridine (30 c.c.) kept at 0°, and, after 30 minutes,

¹² O. *Frehdén* und K. *Fürst*, *Mikrochemie*, 1938, **25**, 256.

¹³ *King, Waley, Abraham, Chain, Baker, and Robinson*, C. P. S. Report No. 88 in C. P.

¹⁴ E. *Fischer* and J. *Schmidlin*, *Liebigs Annalen*, 1905, **340**, 191; E. *Fourneau* and V. *Nicolitch*, *Bull. Soc. chim.*, 1928, **43**, 1239.

the solution was stirred into ice (600 c.c.). When the odour of acetic anhydride could no longer be detected, the solid product was collected, washed with water, and dissolved in ether (100 c.c.). The dried (sodium sulphate) ethereal solution was treated with charcoal (6 g.), filtered through a shallow bed of alumina and evaporated at room temperature under reduced pressure. The residue (5 g.) was dissolved in methanol (75 c.c.) at 40° and crystallized by cooling in an alcohol-solid carbon dioxide bath, affording yellow needles (4.1 g.), m.p. 86—88° after sintering at 80°. This material was sufficiently pure for catalytic reduction.

2-Benzylloxazolone

2-Benzylidenepseudoxazolone (3 g.), dissolved in dry ether (160 c.c.), was hydrogenated at room temperature over Raney nickel at 75 atmospheres for 30 minutes and the resulting solution was filtered and evaporated in vacuo. The residual pale yellow viscous oil (2.5 g.) was treated with dry ether (20 c.c.) and the liquid decanted from the insoluble material (0.5 g.). This solution of 2-benzylloxazolone was found to be sufficiently pure for synthetic purposes. For analysis, a portion was distilled in bulbs yielding a nearly colourless oil, b.p. 90—100° (bath)/0.005 mm. (Found: C, 68.2; H, 5.3; N, 7.6. $C_{10}H_9O_2N$ requires C, 68.6; H, 5.1; N, 8.0%). This oil gave *phenaceturic acid*, m.p. and mixed m.p. 142°, on treatment with water, and the *benzylamide*, m.p. 171 to 172°, and the *anilide*, m.p. 155—157°, on treatment in benzene with benzylamine and with aniline respectively. The substance is readily hydrolysed by moist air and polymerizes rapidly at 100°.

α-Benzylaminophenaceturic Benzylamide

Benzylamine (1 c.c.) was added to a solution of 2-benzylidenepseudoxazolone (0.5 g.) in benzene (10 c.c.) and, after 4 days, the precipitate (0.7 g.), m.p. 139—141°, was collected. A further quantity (0.15 g.) of the same material was obtained by extracting the filtrate with dilute hydrochloric acid. The *compound* separated from benzene-ligroin mixture in colourless prisms, m.p. 142—143° after two recrystallizations (Found: C, 74.2; H, 6.4; N, 10.9. $C_{24}H_{25}O_2N_3$ requires C, 74.4; H, 6.5; N, 10.8%). Treatment of the solid with cold dilute hydrochloric acid converted it to the sparingly soluble hydrochloride which was difficult to recrystallize. The salt regenerated the original substance on basification.

A portion (0.1 g.) of the product was heated with dilute hydrochloric acid (20 c.c.) on a steam bath until all the solid had nearly dissolved (20 minutes). The hot solution was filtered and treated with a solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. After some hours the *2,4-dinitrophenylhydrazone* of glyoxylic benzylamide was collected, purified by chromatographing a chloroform solution on alumina, and crystallized from benzene-ligroin as yellow needles (30 mg.), m.p. 177—178° (Found: C, 52.9; H, 3.9; N, 20.1. $C_{15}H_{13}O_5N_5$ requires C, 52.5; H, 3.8; N, 20.4%).

α-Anilinophenaceturic Anilide

Aniline (1 c.c.) was added to a solution of 2-benzylidenepseudoxazolone (0.5 g.) in benzene (10 c.c.) and, after 3 days, the crystalline product was collected. Two recrystallizations from benzene afforded colourless flakes, m.p. 165—166° (Found: C, 73.6; H, 6.1; N, 11.4. $C_{22}H_{21}N_3O_2$ requires C, 73.5; H, 5.8; N, 11.7%).

Methyl Benzylpenicillanate

A mixture of 2-benzylloxazolone (0.8 g.) in ether (8 c.c.) and 4-carbomethoxy-5,5-dimethylthiazoline (0.8 g.) in dry benzene (10 c.c.) was distilled until the vapour temperature reached 60° and was then refluxed for 20 hours. After evaporation of the solvent in vacuo, alcohol (10 c.c.) was added to dissolve the residue and the resulting solution was diluted with ether (200 c.c.) and filtered. The filtrate was washed with dilute hydrochloric acid, sodium carbonate solution and water, and was then dried and treated with mercuric chloride in ether. The precipitate was collected and the filtrate, after removal of excess mercuric chloride with hydrogen sulphide, was concentrated to about 10 c.c. when a crystalline product (0.6 g.), m.p. 147—148°, separated. Two recrystallizations from alcohol afforded colourless prisms, m.p. 149—150°* not depressed on admixture with an authentic specimen of methyl penicillanate (Found: C, 58.8; H, 5.8; N, 7.85; S, 9.5. Calc. for $C_{17}H_{20}N_2S$: C, 58.6; H, 5.8; N, 8.0; S, 9.2%). Inferior results were obtained when ether was used as a solvent for the reaction.

Decomposition of the mercuric precipitate in the usual manner gave a resin (0.3 g.), showing an absorption maximum at 3100 Å (ϵ , 626). (The Merck group record a maximum at 3100 Å (ϵ , 6,300) for methyl penicillanate¹⁵).

The reaction was also effected in pyridine solution and in ether with the addition of boron trifluoride. Methyl penicillanate was produced in both cases in relatively small amount.

Reaction of Benzalaniline with 2-Phenylloxazolone

(a) *In Pyridine.* Benzalaniline (0.9 g.) and 2-phenylloxazolone (0.8 g., 1 mol.) were dissolved in dry pyridine (10 c.c.). Within 15 minutes the solution began to deposit long yellow needles. After 1 hour these were collected and the filtrate was poured into water. The solid precipitate, so obtained, was collected and extracted with boiling ether, leaving only a small residue (50 mg.) which crystallized from methanol in colourless needles, m.p. 229 to 231° (Found: C, 76.9; H, 5.2; N, 7.9. Calc. for $C_{22}H_{18}O_2N_2$: C, 77.2; H, 5.3; N, 8.2%). The m.p. of the compound was not depressed on admixture with a specimen of α -benzamidocinnamic anilide, prepared by heating 2-phenyl-4-benzaloxazolone in benzene with excess aniline; *Erlenmeyer*¹⁷ records the m. p. 238°. The residue obtained by evaporation of the ethereal extract was combined with the initial crystals and the whole recrystallized from methanol, giving yellow needles (0.9 g.) m. p. 163—164° (Found: C, 76.9; H, 4.5; N, 5.4. Calc. for $C_{16}H_{11}O_2N$: C, 77.1; H, 4.4; N, 5.6%); the m. ps. 159°, 184—185°, 185—188° have been recorded for 2-phenyl-4-benzaloxazolone¹⁶.

When the reaction time is extended the crystals of 2-phenyl-4-benzaloxazolone, formed initially, redissolve and crystals of α -benzamidocinnamic anilide separate from the solution. From an experiment similar to the above, 0.25 g. of the former product and 1 g. of the latter were isolated after 6 days.

(b) *In Ether.* A solution of benzalaniline (0.9 g.) and 2-phenylloxazolone (0.8 g., 1 mol.) in dry ether (30 c.c.) was refluxed for 40 hours. The solid pro-

* The Merck group¹⁵ record m.p. 151—152°, presumably a corrected value.

¹⁵ Merck Report No. 46.

¹⁶ Cf. *Beilstein*, 27, 235.

¹⁷ *Erlenmeyer jun., Ber. dt. Chem. Ges.*, 1900, 33, 2037.

duct was collected and extracted with boiling ether (2×100 c.c.). The filtrate, combined with the ethereal extracts, was evaporated, leaving 2-phenyl-4-benzaloxazolone (0.6 g.). The ether insoluble product (0.5 g.), m.p. 180 to 200° , was crystallized from amyl alcohol (15 c.c.), giving colourless needles (0.2 g.), m.p. $192\text{--}214^{\circ}$, which, after repeated crystallization from pyridine and from methanol, had m.p. $229\text{--}231^{\circ}$, not depressed on admixture with α -benzamidocinnamic anilide. Concentration in vacuo of the amyl alcoholic mother liquor gave a crop of colourless plates (0.1 g.), m.p. $204\text{--}211^{\circ}$, which, after recrystallization from ethanol and from methanol had m.p. $210\text{--}212^{\circ}$ (Found: C, 71.1; H, 5.7; N, 10.8. Calc. for $C_{15}H_{14}O_2N_2$: C, 70.8; H, 5.5; N, 11.0%). The m.p. of the substance was not depressed on admixture with a specimen of hippuric anilide prepared by heating 2-phenyloxazolone with aniline in benzene¹⁷; Curtius records 208.5° for the m.p. of a specimen synthesized from hippuric azide¹⁸.

¹⁸ *Th. Curtius, J. pr. Chem.*, [2] **52**, 257 (1895).