of California material. The injury may be a discolored spot centering on a minute feeding puncture, but in more severe cases or when several such spots coalesce, an open corroded pit is evident in the seed coat and cotyledon. Such injuries have been called aphid spot, yeast spot, or seed pitting by growers and shippers. Accompanying this condiiton is the shedding of blossoms and of pods up to two inches or more in length. The pods which wilt, turn yellow, and abscise are termed "buckskins" by growers and have been attributed to other causes, such as heat injury, or to steaming from irrigation after the vines have covered the ground. Pods containing pitted seeds cannot be detected positively by external examination alone. However, they frequently exhibit internal proliferations and brown areas, some of which contact the pits of the seeds.

These several types of injuries have now been demonstrated to result from the toxic feeding of Lygus bugs (*Lygus hesperus* Knight, *L. elisus* V.D., and perhaps others) on the developing fruiting structures of the Lima bean plant without the involvement of pathogenic microorganisms. It seems desirable at this time to clarify the situation in California, the leading Lima-bean-producing area of the country, and to indicate the impossibility of distinguishing this trouble, solely on the basis of symptoms, from that attributed to yeast.

Pitting of field-bean seeds apparently was first reported (*2*) in Michigan in 1895 and shown to be a result of Lygus feeding. This relationship has been confirmed in New York (*3*) and Idaho (*5*) and has been shown to occur also on the baby Lima bean in the latter state. Specimens of injured California beans submitted to W. E. Shull were said to be identical with those which resulted from Lygus feeding in Idaho. Pitting was reported (*1*) on Lima beans from California in 1922 and was attributed, apparently on the basis of symptoms, to yeast spot. That the seed pitting, and blossom and pod drop of Lima beans in California actually resulted from Lygus feeding was first suspected by the writers following visits to fields in Ventura County in August 1944, and subsequent work has confirmed this relationship. Such injury has been observed on large and baby Lima bean and black-eyed cowpea, but not on common bean.

Fields with severe blossom and pod drop tend also to have abundant seed pitting and, in Ventura County, a high incidence of Lygus bugs. In some areas, however, the Lygus populations late in the season may become too low to account for the evident damage initiated earlier. The injury has been worst in fields adjacent to seed beets and to alfalfa, particularly after it is cut. Damage also has been worst in parts of Lima bean fields closest to these established, favorable hosts of the insects, and within such areas the loss commonly diminishes with distance. The first crop of pods are not usually injured, but with the high Lygus populations of midsummer, much pod shedding and seed pitting occurs.

Lygus bugs commonly feed on flowers and fruits or seeds and are known to cause severe blossom drop on alfalfa (*8, 9*) and cotton (*6*) and to reduce germination of beet seed (*4*); they have been shown (*7*) to be highly toxicogenic. The observed facts in California are in accord with published data on the injuries produced by these insects on various plants, including common and Lima beans.

Experiments in which Lygus bugs were caged on plants in the field and on individual pods in the greenhouse fully confirmed the fact that they produced the various types of injury. Dropping of blossoms and young pods always resulted, and on older pods the internal proliferations and typical pitting of the seed occurred within seven days. Checks remained uninjured. There was no evidence of yeast or other microorganisms in the tissues.

The results establish the fact that the toxic feeding of Lygus bugs is responsible in the California Lima bean crop for a seed spotting and pitting, and for some of the dropping of blossoms and pods. It is possible that other insects also may be involved. Details are being published elsewhere.

References

1. Anderson, H. W. *Phytopathology*, 1924, **14**, 31.
2. Davis, G. C. *Mich. St. Bd. Agric., Ann. Rep.*, 1897, **55**, 136.
3. Hawley, I. M. *N. Y. (Cornell) agric. exp. Sta. Mem. 55*, 1922.
4. Hills, O. A. *J. agric. Res.*, 1943, **67**, 389–394.
5. Shull, W. E. *Ida. agric. exp. Sta. Res. Bull. 11*, 1933.
6. Smith, G. L. *Calif. agric. exp. Sta. Bull. 660*, 1942.
7. Smith, K. M. *Ann. appl. Biol.*, 1920, **7**, 40–55.
8. Smith, R. F., and Michelbacher, A. E. *Calif. St. Dept. Agric. Bull.*, 1944, **33**, 39–52.
9. Sorenson, C. J. *Ut. agric. exp. Sta. Bull. 284*, 1939.
10. Wingard, S. A. *Phytopathology*, 1922, **12**, 525–532; *Bull. Torrey bot. Club*, 1925, **52**, 249–290.

Oral Penicillin X [1]

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A brief resumé of some of the properties of penicillin X and the results of a clinical trial in gonorrhea were recently published by workers of the Food and Drug Administration (*4*). It was shown that, unit for unit, penicillin X is superior to the usual commercial preparations of penicillin in acute gonorrhea and in protecting mice against pneumococcal infec-

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tion. Simultaneous *in vitro* tests were carried out in this laboratory with commercial lots consisting almost entirely of penicillin G and with preparations containing 65 per cent or more of penicillin X. Most strains of Group A hemolytic streptococci, gonococci, and meningococci were from two to eight times more sensitive to penicillin X; most strains of pneumococcus and of *Streptococcus viridans* were twice as sensitive to penicillin X, and most of the staphylococci were equally sensitive to both forms of penicillin. Levels of penicillin activity in the serum against Strep. 98 were studied and found to be significantly higher and to be sustained longer after intramuscular injections of penicillin X than after injections of the same number of units of regular penicillin in the same subjects (*2*).

Similar studies of the levels of penicillin activity in the serum after oral administration of the two kinds of penicillin have also been carried out. The results were strikingly different and are the subject of the present report.

The methods used and the injectable preparations of penicillin X were the same as in the previous studies (*2*). In addition, tablets of regular calcium penicillin and of penicillin X, each containing about 30,000 I.U. (*3*) with certain adjuvants, were also available for these studies.[2] Subjects A, B, and C were members of the laboratory staff; D, E, and F were hospital patients who had no recent infections and had not recently received penicillin or sulfonamides, but subject F had a duodenal ulcer with normal gastric acidity; and subjects G, H, and I were cases of pernicious anemia with gastric anacidity after histamine injections. All of the oral doses consisted of 90,000 units and were given one-half hour before breakfast. Previous studies have shown that higher, better-sustained, and more uniform serum levels are obtained when oral doses are given before meals (*1*).

The results are shown in Fig. 1. In interpreting these results it must be borne in mind that Strep. 98, the strain used in determining the serum levels, was found to be from two to four times more sensitive to the preparations of penicillin X than to the commercial penicillin used in the present studies. The unitage as recorded on the chart is based on the sensitivity of Strep. 98 to penicillin G: 0.02 and 0.03 units represent complete killing of 10,000 streptococci contained in 0.5 cc. and 0.2 cc., respectively, of undiluted serum, and the other values are based on serial twofold dilutions of 0.2 cc. of serum. The same values are recorded for regular penicillin and for penicillin X.

[2] Injectable penicillin X was supplied by Lederle Laboratories, Inc., and by Cutter Laboratories, the former also providing the tablets of penicillin X. Tablets of regular calcium penicillin were furnished by Hoffmann-La Roche, Inc. Commercial preparations of several brands of regular sodium penicillin were used for solutions.

In each of the six subjects who received the two kinds of penicillin in solution, the effective serum levels were significantly higher and were sustained better when regular penicillin was given. Comparable differences were observed in the normal subjects and in the cases of pernicious anemia. When the tablets

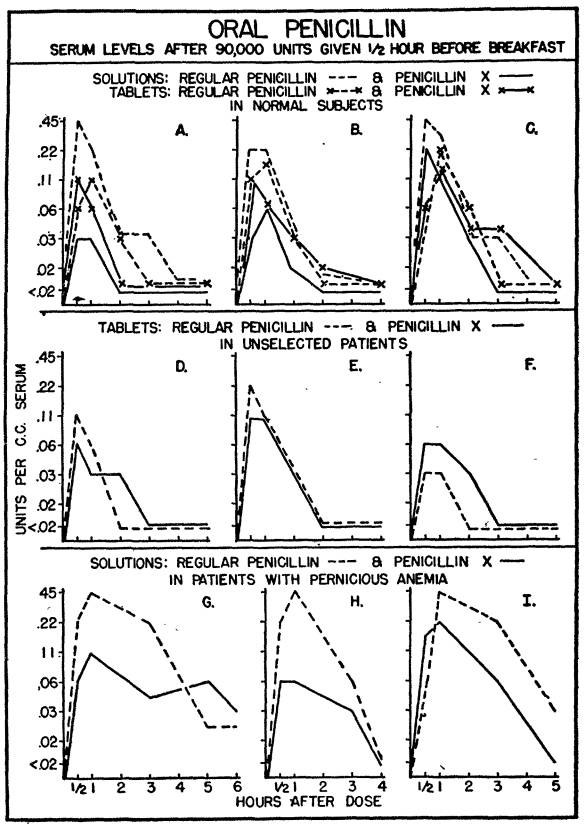

FIG. 1

were given, there was no constant or significant difference in the serum levels after the two kinds of penicillin. Except in subject F, however, the maximum serum levels after the regular penicillin were the same or higher than those obtained after penicillin X. As in the previous study (*1*), higher and more sustained levels from oral doses were obtained in the achlorhydric subjects. In view of the greater sensitivity of the test strain of streptococcus, the higher values obtained after the regular penicillin assume an even greater significance than is apparent from the values shown in the chart.

Conclusions. When measured with Strep. 98, an organism which is two to four times more sensitive to penicillin X than to regular penicillin, the effective levels of penicillin activity in the serum were found to be higher in the same subjects after regular penicillin than after comparable preparations of penicillin

X, each given orally. The results are in sharp contrast to those obtained after intramuscular injections of these two kinds of penicillin and suggest that penicillin X is not absorbed as well as penicillin G after oral administration.

References

1. FINLAND, MAXWELL, MEADS, MANSON, and ORY, E. M. *J. Amer. med. Ass.*, 1945, **129**, 315.
2. ORY, E. M., MEADS, MANSON, and FINLAND, MAXWELL. *J. Amer. med. Ass.*, 1945, **129**, 257.
3. VELDEE, M. N., HERWICK, R. P., and COGHILL, R. B. *Science*, 1945, **101**, 42.
4. WELCH, HENRY, PUTNAM, L. E., RANDALL, W. A., and HERWICK, R. P. *J. Amer. med. Ass.*, 1944, **126**, 1024; VANWINKLE, W., JR., and HERWICK, R. P. *J. Amer. pharm. Ass.* (Sci. ed.), 1945, **34**, 97.

The Beckmann Rearrangement of Aliphatic Ketoximes

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Sidgwick (*8*) states that the Beckmann transformation of methyl *n*-propyl ketoxime results in the formation of two amides, whereas the analogous rearrangement of methyl isopropyl ketoxime gives but one. From this he argues for the existence of steric interaction between the hydroxyl and isopropyl groups of the latter oxime, which would prevent the formation of the alternate amide. This argument cannot hold, because of an apparent oversight in previous literature. Although Beilstein (*1*) gives the above information concerning the two rearrangements, reference to the original paper (*4*) shows that in all cases investigated all possible products were formed from

$$CH_3\text{–}C(=NOH)\text{–}R \qquad I$$

where R may be propyl or isopropyl as well as ethyl or hexyl. In each of these cases the amide with the configuration

$$CH_3\text{–}CONH\text{–}R \qquad II$$

was found in the greater proportion, but lesser amounts of $R\text{–}CONH\text{–}CH_3$ were also detected in every instance. Thus, the statement by Sidgwick, "It is unlikely that the electrical fields of the propyl and isopropyl groups are widely different, but the space they occupy in the vicinity of the oxime hydroxyl group must differ," is not necessarily relevant. Kharasch (*9*) has demonstrated that the electrical fields of the methyl, propyl, and isopropyl groups do differ enough to direct the course of certain reactions. Hence, the relative electronegativity of CH_3– as compared with that of R may still be a deciding factor on the course of the rearrangement. This consideration of oximes (I) with R as propyl or isopropyl is important where prediction is to be applied to the course of rearrangement of 2-alkylcyclohexanone oximes (III)

$$\begin{array}{l} CH_2-CH_2-C=NOH \\ \quad\quad\quad\quad\quad\quad\quad | \\ CH_2-CH_2-CHR \end{array} \qquad III$$

where R may also be methyl. The similarity in structure of (I), where R is isopropyl and (III), where R is methyl, is obvious from the formulas. In most of these cases (*6, 7, 10*) only one of the two possible products is found. However, at least one exception has been found (*11*) which now no longer seems anomalous in view of the corrected statement of earlier findings for methyl isopropyl ketoxime. Unfortunately, no quantitative information was given by Wallach for 2,4,4-trimethylcyclohexanone oxime (*11*), and the identity of the products was not established.

Higman (*5*) has recently presented a mechanism for the Beckmann rearrangement which does not involve the classical migration of groups (see chapter on the Beckmann rearrangement, *8*) but only a 90° twist by C=N in an oxime, followed by a small angular displacement of substituents. With the electronegativity considerations of Degering (*2*) in mind, we may look upon the segment C=N as a dipole with a relatively positive nitrogen atom. The minimum rotation of C=N would then be preferred in the direction of the more negative (greater electron releasing) R rather than toward methyl or methylene (*9*), although some product from the alternate course of reaction would be expected and has been found (*4, 11*). Through similar qualitative considerations Degering was able to predict the course of the reaction of 2-alkylcyclohexanone oximes (*3*) whereby products similar to (II) were formed. It is hoped that this discussion will help to tie together the early and recent work on the rearrangement of aliphatic ketoximes.

References

1. BEILSTEIN. *Handbuch der organischen Chemie.* Leipzig: Julius Springer, 1918. Vol. 1, p. 683.
2. DEGERING, E. F. *Ind. Acad. Sci.*, 1942, **52**, 135.
3. DEGERING, E. F. Private communication, 8 July 1944.
4. HANTZSCH, A. *Ber.*, 1891, **24**, 4018.
5. HIGMAN, B. *Nature, Lond.*, 1945, **156**, 242.
6. HILDEBRAND, J. G., and BOGERT, M. T. *J. Amer. chem. Soc.*, 1936, **58**, 650.
7. MCLAREN, A. D., and PITZL, G. *J. Amer. chem. Soc.*, 1945, **67**, 1625.
8. SIDGWICK, N. V. *The organic chemistry of nitrogen.* London: Oxford Univ. Press. 1937. P. 191.
9. TOWNE, E. B. *Synth. org. Chem.*, 1944, **16**, No. 4.
10. UNGNADE, H. E., and MCLAREN, A. D. *J. org. Chem.*, 1945, **10**, 29.
11. WALLACH, O. *Ann. Chem.*, 1906, **346**, 258.