Infrared analysis showed the complete disappearance of the 6.3 peak and the appearance of a strong peak at 6.84 to 6.89 μ, $[\alpha]_D$ −54.7° (c 2 in MeOH), neut. equiv. 692 (theory 720), pK_a 8.2 (in 50% ethanol).

Sodium Periodate Oxidation of the Hydrolysis Product XI.—One gram of compound XI was oxidized with 1.3 g. of sodium periodate in 100 ml. of water at 50°. The volatile aldehydes were recovered by blowing a nitrogen stream through the solution and bubbling the outgoing gases through a solution of 2,4-dinitrophenylhydrazine. The precipitating aldehyde derivative was filtered and crystallized from ethanol–water, m.p. 157–159°, identical with acetaldehyde 2,4-dinitro-phenylhydrazone in mixed melting point, paper chromatographic migration and infrared spectrum.

BROOKLYN 6, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

γ-Ketophosphonic Acid Derivatives in the Indole Series[1]

BY J. SZMUSZKOVICZ

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The Mannich base methiodide (I) in the 3-acylindole series was shown to give rise to the diethyl γ-keto-propylphosphonate derivative (V) on nucleophilic substitution with triethyl phosphite. During alkaline hydrolysis of V, monosaponification and N-ethylation occurred. The resulting monobasic acid XII afforded a γ-keto-propylphosphonic acid which in the solid state was stable in the lactol form XVII. The behavior of 1-alkyl (II and III) and 5-benzyloxy (IV) Mannich bases was examined and the reactions extended also to trimethyl and triisopropyl phosphite.

γ-Ketophosphonic acid derivatives have been prepared recently employing the methiodide or hydrochloride of a β-diethylamino ketone and triethyl phosphite.[2] This reaction constitutes an extension of the Michaelis–Arbuzov reaction,[3] for which we propose the name "the Jensen reaction."

Another general method involves the treatment of α,β-unsaturated ketones with dialkyl phosphites and sodium methoxide in methanol.[4]

This paper describes the application of the "Jensen reaction" to Mannich bases of certain indolyl ketones. On refluxing with triethyl phosphite, 1-(3′-indolyl)-3-dimethylaminopropan-1-one methiodide (I)[10b] afforded in good yield diethyl γ-(3-indolyl)-γ-ketopropyl phosphonate (V)[5] which showed NH absorption in the infrared spectrum and a band of the vinylogous amide grouping common to the 3-acylindole derivatives (1634–1645 cm.$^{-1}$).

As attempted acid hydrolysis of V led to considerable decomposition, our attention was turned to the alkaline treatment.[6]

When heated with aqueous potassium hydroxide, V was converted to a monobasic acid, ethyl γ-keto-γ-[3-(1-ethyl)-indolyl]-propylphosphonate (XII) (along with about 8% of the N-unethylated material; see Experimental), which exhibited amide but no NH absorption in the infrared spectrum. It became evident that, during the alkaline hydrolysis, ethylation of the indole nitrogen occurred, the diethyl phosphonate acting as the alkylating agent.[7] Although the question of the molecularity of this O → N alkyl transfer was not investigated, molecular models appear not to exclude the interesting possibility of this being an intramolecular reaction.

An alternative method for the preparation of XII starts with 1-[3′-(1′-ethyl)-indolyl]-3-dimethylaminopropan-1-one methiodide (II).[10b] When II was subjected to the reaction with triethyl phosphite, diethyl γ-[3-(1-ethyl)-indolyl]-γ-keto-propylphosphonate (VI) was obtained which on alkaline hydrolysis afforded XII identical with the compound obtained starting with I. This method is superior to the first if a purer form of XII is desired.

On recrystallization from water, XII was converted to a new compound (XVII), which was soluble only in polar solvents. Compound XVII was a dibasic acid, showed typical 3-acylindole absorption in the ultraviolet spectrum in ethanolic solution, but no amidic band in the infrared (Nujol). The monosodium salt of XVII, on the other hand, exhibited an amidic band in infrared at 1637 cm.$^{-1}$. Acid XVII, therefore, *exists in the solid state* in the lactol form of the corresponding γ-[3-(1-ethyl)-indolyl]-γ-keto-propylphosphonic acid and is, to our knowledge, the first compound of its class in the γ-ketophosphonic acid series.[8]

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(1) Presented at the 131st Meeting of the American Chemical Society, Miami, Fla., April, 1957; Abstracts p. 55-O.

(2) T. C. Myers, R. G. Harvey and E. V. Jensen, THIS JOURNAL, **77**, 3101 (1955).

(3) For a general review of the Michaelis–Arbuzov reaction see G. M. Kosolapoff, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 276; G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 197.

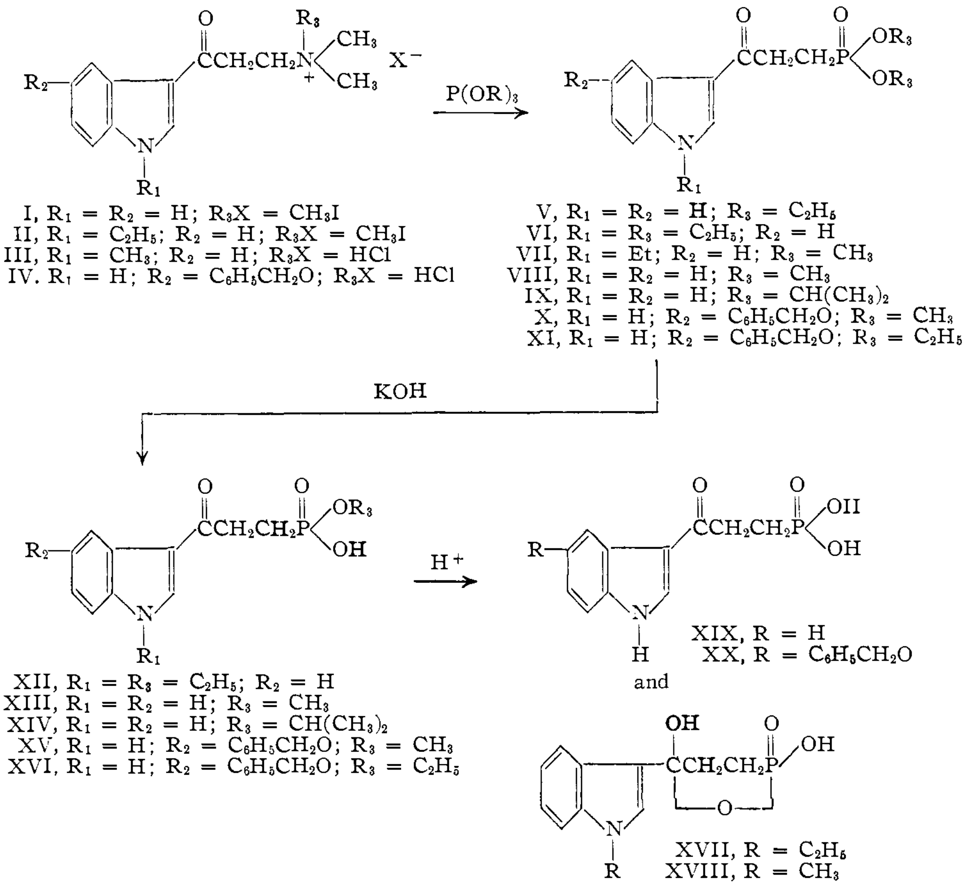
(4) A. N. Pudovik, *J. Gen. Chem.*, **22**, 525 (1952), in English translation; *C. A.*, **47**, 2686 (1953), and previous references.

(5) The structures of the phosphonate derivatives are formulated with a P=O bond on the basis of Raman data in the literature and the tentative assignment of the infrared band in the 1250 cm.$^{-1}$ region to the P=O stretching vibrations. For leading references see L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., London, 1954, p. 258. It is the hope of the organic chemist that a more definite answer to this problem will evolve from nuclear magnetic resonance studies. For a recent paper in this field see W. Muller, P. C. Lauterbur and J. Goldenson, THIS JOURNAL, **78**, 3557 (1956).

(6) *Cf.* J. Kennedy and R. V. Davies, *Chemistry & Industry*, 378 (1956); B. S. Griffin and A. Burger, THIS JOURNAL, **78**, 2336 (1956); N. Mikhailova, *C. A.*, **40**, 555 (1946); M. Janczak, *Rocz. Chem.*, **6**, 774 (1926); *C. A.*, **21**, 3599 (1927); A. F. Torralba and T. C. Myers, *J. Org. Chem.*, **22**, 972 (1957).

(7) It is well known that 3-acylindoles undergo N-alkylation on treatment with dialkyl sulfates and alkali; *e.g.*, 1-methyl- and 1-ethyl-3-acetylindole are obtained in 95 and 98% yield, respectively, according to Y. A. Baskakov and N. N. Mel'nikov, *C. A.*, **49**, 1006 (1955). The alkylating properties of esters in the phosphorus acid series have been demonstrated in many instances in the case of esters of phosphoric acid; for references see F. R. Atherton, *Quart. Rev.*, **3**, 151 (1949). The alkylation of 2-aminofluorene with diethyl ethanephosphonate has been described by T. L. Fletcher, M. E. Taylor and A. W. Dahl [*J. Org. Chem.*, **20**, 1021 (1955)] and esterification of carboxylic acids with dialkyl phosphonates by F. W. Hoffmann and H. D. Weiss, THIS JOURNAL, **79**, 4759 (1957).

(8) Pseudo esters of γ-oxocarboxylic acids are well known [see ref. 6 in the paper by M. S. Newman and C. D. McCleary, *ibid.*, **63**, 1537 (1941)]. A method of determining proportion of free acid



I, $R_1 = R_2 = H$; $R_3X = CH_3I$
II, $R_1 = C_2H_5$; $R_2 = H$; $R_3X = CH_3I$
III, $R_1 = CH_3$; $R_2 = H$; $R_3X = HCl$
IV, $R_1 = H$; $R_2 = C_6H_5CH_2O$; $R_3X = HCl$

V, $R_1 = R_2 = H$; $R_3 = C_2H_5$
VI, $R_1 = R_3 = C_2H_5$; $R_2 = H$
VII, $R_1 = Et$; $R_2 = H$; $R_3 = CH_3$
VIII, $R_1 = R_2 = H$; $R_3 = CH_3$
IX, $R_1 = R_2 = H$; $R_3 = CH(CH_3)_2$
X, $R_1 = H$; $R_2 = C_6H_5CH_2O$; $R_3 = CH_3$
XI, $R_1 = H$; $R_2 = C_6H_5CH_2O$; $R_3 = C_2H_5$

XII, $R_1 = R_3 = C_2H_5$; $R_2 = H$
XIII, $R_1 = R_2 = H$; $R_3 = CH_3$
XIV, $R_1 = R_2 = H$; $R_3 = CH(CH_3)_2$
XV, $R_1 = H$; $R_2 = C_6H_5CH_2O$; $R_3 = CH_3$
XVI, $R_1 = H$; $R_2 = C_6H_5CH_2O$; $R_3 = C_2H_5$

XIX, R = H
XX, $R = C_6H_5CH_2O$
and

XVII, $R = C_2H_5$
XVIII, $R = CH_3$

Esterification of XVII with excess diazomethane afforded the normal dimethyl ester dimethyl γ-keto-γ-[3-(1-ethyl)-indolyl]-propylphosphonate (VII) which was identical with the product obtained on treatment of II with trimethyl phosphite.

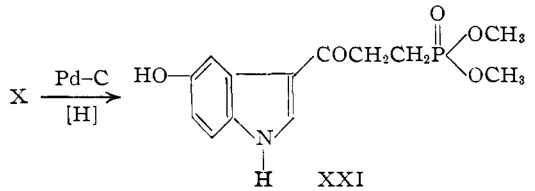
When the starting compound was 1-[3′-(1′-methyl)-indolyl]-3-dimethylaminopropan-1-one hydrochloride (III),[10b] the lactol form of γ-[3-(1-methyl-indolyl]-γ-keto-propylphosphonic acid (XVIII) was isolated after successive treatments with triethyl phosphite, potassium hydroxide and recrystallization from acetic acid.

The reaction of I with trimethyl phosphite gave rise to dimethyl γ-(3-indolyl)-γ-ketopropylphosphonate (VIII). Alkaline hydrolysis of VIII gave rise to a mixture in which the unalkylated product, namely, methyl γ-(3-indolyl)-γ-ketopropylphosphonate (XIII), predominated. The composition of this mixture was determined by esterification with diazomethane whereupon some of the dimethyl ester VIII was isolated. The oily residue was examined quantitatively in the NH region of the infrared and led to the conclusion that the total alkaline hydrolysis mixture contained 79% of XIII. The rest of the material was most likely the corresponding N-methylated compound. Treatment of the crude alkaline hydrolysis mixture with dilute acetic acid—followed by fractional crystallization—gave rise to γ-(3-indolyl)-γ-ketopropylphosphonic acid (XIX).

Similar series of reactions starting with I and triisopropyl phosphite afforded diisopropyl γ-(3-indolyl)-γ-ketopropylphosphonate (IX) which on alkaline hydrolysis gave *exclusively* isopropyl γ-(3-indolyl)-γ-ketopropylphosphonate (XIV). On hydrolysis with dilute hydrochloric acid XIV was converted to XIX which was identical with the product obtained from VIII.

The reaction of 1-[3′-(5′-benzyloxy)-indolyl]-3-dimethylaminopropan-1-one hydrochloride (IV) and trimethyl phosphite gave rise to dimethyl γ-[3-(5-benzyloxy)-indolyl]-γ-ketopropylphosphonate (X).

Hydrogenolysis of X in ethanol in the presence of palladium afforded dimethyl γ-[3-(5-hydroxy)-indolyl]-γ-ketopropylphosphonate (XXI).



XXI

Alkaline hydrolysis of X and treatment of the resulting methyl γ-[3-(5-benzyloxy)-indolyl]-γ-ke-

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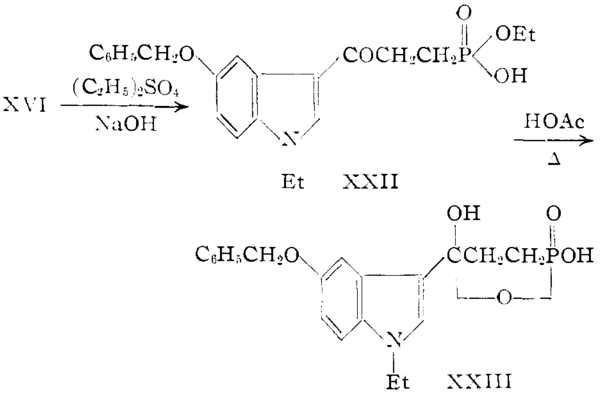
which exists in the lactol form has been developed by M. S. Newman and C. W. Muth, *ibid.*, **73**, 4627 (1951). There are a number of cases where the γ-oxocarboxylic acids exist in the lactol form in the solid state, *e.g.*, gladiolic acid [J. F. Grove, *J. Chem. Soc.*, 3345 (1952); J. J. Brown and G. T. Newbold, *ibid.*, 1076 (1954); J. Blair, W. R. Logan and G. T. Newbold, *ibid.*, 2443 (1956)] and the autoxidation product of menthofuran [R. B. Woodward and R. H. Eastman, THIS JOURNAL, **72**, 399 (1950) and also references 6 and 7 cited therein]. The ozonization product of pyrene is stable in the lactol form both in the solid form and in solution [M. S. Newman and H. S. Whitehouse, *ibid.*, **71**, 3664 (1949) and private communication from Professor M. S. Newman].

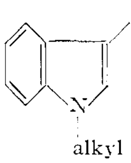
topropylphosphonate (XV) with acetic acid afforded γ-[3-(5-benzyloxy)-indolyl]-γ-ketopropylphosphonic acid (XX).

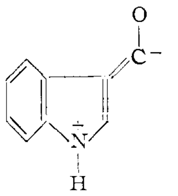
Similarly, reaction of IV and triethyl phosphite afforded the diethyl ester XI which was converted to the monoethyl ester XVI and the phosphonic acid XX.

Treatment of XVI with diethyl sulfate in alkaline solution gave rise to the N-ethylated compound XXII, which was converted by boiling acetic acid to the lactol of γ-[3-(1-ethyl-5-benzyloxy)-indolyl]-γ-ketopropylphosphonic acid (XXIII).

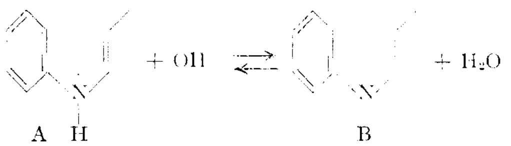


The above results provide the basis for the following conclusions: (a) γ-(3-indolyl)-γ-ketopropylphosphonic acid exists in the solid state in the lactol form when the indole nitrogen is substituted by an alkyl group bringing about the predominance of the keto form XXIV and decrease in amidic character


XXIV


XXV

of the 3-acylindole system. When NH is present, the acid exists in the solid state in the open form due to the enol XXV predominating.[9] (b) During alkaline hydrolysis of dialkyl γ-(3-indolyl)-γ-ketopropylphosphonate N-alkylation occurs more readily with diethyl than with dimethyl and not at all with the diisopropyl ester. When the ester bears a 5-benzyloxy substituent in the indole ring no alkylation occurs. It would then appear that simple hydrolysis and intramolecular alkylation of nitrogen compete with one another during the alkaline treatment. The balance between these two competing processes seems to be affected both by steric and electronic factors, possibly in the following way. The starting material probably consists of an acid–base equilibrium mixture of the following type, in which B is the species which undergoes intramolecular alkylation.



The contrasting relative rates of the two reactions in the cases where the alkyl group is methyl, ethyl and isopropyl would seem to represent different sensitivity of the intra- and intermolecular processes to steric effects. The intramolecular S$_N$2 reaction might be expected to differ only slightly in passing from methyl to ethyl, but be slowed considerably in the case of the isopropyl group, whereas the hydrolytic reaction might slow down by more even increments in passing from methyl to ethyl to isopropyl. Thus, in the case of the diethyl ester, the substitution reaction might dominate, whereas hydrolysis predominates in the case of the dimethyl and diisopropyl esters. When the benzyloxy group is substituted in the 5-position, the intramolecular alkylation is eliminated. In this case, the electron-releasing character of the benzyloxy group might shift the equilibrium so as to decrease the concentration of B to the point where the intramolecular substitution reaction effectively disappears.

Experimental[10a,b,c]

Condensation of 1-(3′-Indolyl)-3-dimethylaminopropan-1-one Methiodide (I)[10b] with Triethyl Phosphite.—A mixture of 21.4 g. (0.06 mole) of the methiodide I and triethyl phosphite (100 g., 0.6 mole) was refluxed gently for 3 hours (bath temperature 185–195°). A crystalline precipitate collected in the upper part of the flask and in the mouth of the condenser, and a clear yellow solution was obtained. The mixture was allowed to cool to room temperature, 100 ml. of benzene was added and the suspension was allowed to stand at room temperature overnight. It was then filtered and the precipitate washed with benzene (10.7 g., 83% yield of trimethylethylammonium iodide). The precipitate was recrystallized from methanol–acetone–ether; m.p. 309°, mixed m.p. with authentic trimethylethylammonium iodide (m.p. 310°) 309–310°. The infrared spectra of the two samples were identical.

The benzene filtrate was washed twice with cold water, once with saturated aqueous salt solution, dried over magnesium sulfate and evaporated under reduced pressure, and finally at 0.1 mm. in order to remove triethyl phosphite. A quantitative yield of crude diethyl γ-(3-indolyl)-γ-ketopropylphosphonate (V) was obtained as a yellow oil, the infrared spectrum of which was identical with that of the crystalline material obtained below.

Attempted distillation of V at 0.1 mm. resulted in decomposition. The compound crystallized on standing for a few weeks and after two recrystallizations from chloroform ether, elongated needles were obtained, m.p. 106–108.5°; infrared spectrum: NH (3140 cm.$^{-1}$); vinylogous amide C═O (1645); C═C (1600, 1582, 1529, 1500); P═O (1215); P–O (1040, 975); *o*-disubstituted benzene (790, 744);

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[9] The 1640 cm.$^{-1}$ band which is present in the N-alkyl and NH 3-acylindole compounds described in this paper is undoubtedly due to C═O absorption in the former case. But this may not necessarily be the case in the latter since it *may* be due to —N═C— absorption which is present in the enolic form. This question is still unresolved; see *e.g.*, L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 180–183, and H. M. Randall, N. Fuson, R. E. Fowler and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, pp. 10–13.

[10] (a) All melting points are uncorrected. Ultraviolet spectra were determined in 95% ethanol using Cary spectrophotometers, models 11 and 14. Infrared spectra were determined in Nujol (except when otherwise specified) using a Perkin–Elmer recording infrared spectrophotometer, model 21. (b) The synthesis of I, II and VIII from 3-acetylindole, 1-ethyl- and 1-methyl-3-acetylindole, respectively, by condensation with dimethylamine hydrochloride and paraformaldehyde will be described in a forthcoming paper. (c) Acknowledgments: The author is indebted to Dr. M. S. Newman and Dr. D. J. Cram for stimulating discussions, to Dr. J. L. Johnson and his staff, particularly Mrs. G. S. Fonken, for spectral data, to Mr. W. A. Struck and his associates for microanalyses and neut. equiv. determinations, and to Mr. L. G. Laurian for laboratory assistance.

ultraviolet spectrum: λ_{max} 242 mμ (12,725); flex 260 (8,750); λ_{max} 299 (12,250).

Anal. Calcd. for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53; P, 10.01. Found: C, 57.88; H, 6.62; N, 4.42; P, 10.04.

Hydrolysis of V to Ethyl γ-Keto-[3-(1-ethyl)-indolyl)-propylphosphonate (XII).—A mixture of V (crude oil, 0.03 mole) and a solution of potassium hydroxide (16.8 g., 0.3 mole) in 95 ml. of water was heated on the steam-bath with stirring for 7 hours. A clear yellow solution was obtained after the first hour of heating. After standing at room temperature overnight, it was cooled in ice and acidified with 29 ml. of concentrated hydrochloric acid diluted with 25 ml. of water. The resulting yellow oil was extracted thrice with chloroform. The chloroform extracts were washed successively with water and saturated aqueous salt solution and dried over magnesium sulfate. The solution was then evaporated *at room temperature* under reduced pressure; 7.1 g. of deep yellow oil was obtained which afforded an oily solid on standing overnight. Quantitative infrared comparison of this oily solid (in 2% chloroform solution) with pure XII (m.p. 118.5–119.5°, obtained from II; see below) and pure V (m.p. 106–108.5°) showed the presence of *ca.* 8% NH absorption in the crude sample, indicating incomplete ethylation.

Direct crystallization of the crude XII from methanol–ether–petroleum ether (30–60°) followed by ethyl acetate–ether afforded (with considerable loss) a sample which was identical with pure XII (mixed m.p., infrared, analysis).

Lactol of γ-Keto-γ-[3-(1-ethyl)-indolyl]-propylphosphonic Acid (XVII).—The crude alkaline hydrolysis product XII (7.1 g.) obtained from 0.03 mole of V was extracted with 125 ml. of boiling water, filtered from dark oily material and allowed to crystallize yielding a pink solid (4.4 g., 52% yield based on crude V), m.p. 83–85°, resolidifying and remelting at 170–172°. Recrystallization from water afforded pink needles, m.p. 173–174°; infrared spectrum: bonded OH (2600, 2240); in the 6μ region: 1556, 1530 1490; P=O (1226); P–O (987); *o*-disubstituted benzene (747, 741); ultraviolet spectrum: λ_{max} 245 (13,800); 304 (14,800).

Anal. Calcd. for $C_{13}H_{16}NO_4P$: C, 55.52; H, 5.74; N, 4.98; P, 11.01; neut. equiv., 140.6. Found: C, 55.68; H, 6.19; N, 5.13; P, 10.90; neut. equiv., 136.8.[11]

The same compound (XVII) was obtained by a similar treatment of pure monoester XII (m.p. 118.5–119.5°) with boiling water.

Sodium Salt of γ-Keto-γ-[3-(1-ethyl)-indolyl]-propylphosphonic Acid.—Compound XVII (70 mg.) was dissolved in 3 ml. of water containing 14.6 mg. of anhydrous sodium carbonate. The solution was evaporated at 0.1 mm. at room temperature and the resulting hygroscopic solid dried at 60° overnight; infrared spectrum: vinylogous amide C=O (1637); C=C (1610, 1574, 1526, 1484); P=O (1215); P–O (1145, 1126, 1055); *o*-disubstituted benzene (740).

Condensation of 1-[3′-(1′-Ethyl)-indolyl]-3-dimethylaminopropan-1-one Methiodide (II)[10b] with Triethyl Phosphite.—A mixture of 11.2 g. of the methiodide II (0.03 mole) and 50 g. of triethyl phosphite (0.3 mole) was refluxed (bath temperature, 190–200°) for 2 hours. Some precipitate collected in the mouth of the condenser, but most of it was present in suspension. The mixture was cooled, diluted with 100 ml. of benzene and allowed to stand overnight. It was then filtered and the precipitate, after washing with benzene and drying, amounted to 6.4 g. (99% yield). It melted at 308–309°, and mixed m.p. with authentic trimethylethylammonium iodide (m.p. 310°) showed no depression. The benzene filtrate was washed once with cold water, twice with saturated aqueous salt solution, dried over sodium sulfate and evaporated on the steam-bath under reduced pressure and finally at 0.3 mm. to give diethyl γ-[3-(1-ethyl)-indolyl]-γ-ketopropylphosphonate as a yellow oil (VI), 9.0 g. (89% yield). The oil (1.3 g.) was distilled from an oil-jacketed flask at 0.01 mm. (bath temperature, 210–225°). A pale yellow oil was obtained (1.2 g.), $n^{25}D$ 1.5549; infrared spectrum: vinylogous amide C=O (1645); C=C (1614, 1575, 1527, 1487); P=O (1243, 1227); P–O (1035, 960); *o*-disubstituted benzene (747); ultraviolet spectrum: λ_{max} 245.5 (13,875); 305.5 (15,075).

Anal. Calcd. for $C_{17}H_{24}NO_4P$: C, 60.52; H, 7.17; N, 4.15; P, 9.18. Found: C, 59.95; H, 7.39; N, 4.17; P, 8.99.

Alkaline Hydrolysis of VI to XII.—A mixture of VI (0.8 g.) and a solution of 2.64 g. of potassium hydroxide in 7.92 ml. of water was refluxed with stirring for 7 hours. The resulting solution was cooled in ice, acidified with 4.6 ml. of concentrated hydrochloric acid and worked up in a manner similar to that for compound V. The resulting pale yellow chloroform solution was evaporated *at room temperature* under reduced pressure to give a yellow solid, 0.673 g. (92% yield), m.p. 103–105°. Two recrystallizations from chloroform–petroleum ether (30–60°) gave needles, m.p. 118.5–119.5°, unchanged on further recrystallization; infrared spectrum: bonded OH (2600, 2260); vinylogous amide C=O (1634); C=C (1610, 1560, 1529, 1484); P=O (1224); P–O (1125, 1032, 1005); *o*-disubstituted benzene (735); ultraviolet spectrum: λ_{max} 244 (14,200); 302 (15,175).

Anal. Calcd. for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53; P, 10.01; neut. equiv., 309.29. Found: C, 58.32; H, 6.62; N, 4.75; P, 9.88; neut. equiv., 310.0.[12]

Dimethyl γ-Keto-γ-[3-(1-ethyl)-indolyl]-propylphosphonate (VII).—Compound XVII (0.6 g., 2.12 mmoles) was added to an ethereal solution of diazomethane (70 ml.) prepared from 3 g. of N-methyl-N-nitroso-N′-nitroguanidine.[13] The solid dissolved in a few minutes and after 1.5 hours the solution was evaporated *in vacuo* to about 35 ml., filtered, then evaporated to about 15 ml. and allowed to crystallize (seeding), m.p. 71–73° (0.559 g., 85.5% yield). Recrystallization from ether afforded well defined pale yellow plates, m.p. 71–73°; infrared spectrum: 1693 (probably due to crystal form since this band is absent in chloroform solution); vinylogous amide C=O (1640); C=C (1610, 1573, 1522, 1483); P=O (1255, 1223); P–O (1048, 1016); *o*-disubstituted benzene (752); ultraviolet spectrum: λ_{max} 245.5 (13,625); 305 (14,725).

Anal. Calcd. for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53; P, 10.01. Found: C, 58.02; H, 6.54; N, 4.46; P, 10.16.

Synthesis of VII by Condensation of 1-[3′-(1′-Ethyl)-indolyl]-3-dimethylaminopropan-1-one Methiodide (II)[10b] with Trimethyl Phosphite.—A mixture of II (7.45 g., 0.02 mole) and trimethyl phosphite (24.8 g., 0.2 mole) was refluxed (bath temperature, 150–172°) for 3 hours. The suspension was cooled and 50 ml. of benzene added. Filtration afforded 3.4 g. (80% yield) of tetramethylammonium iodide, m.p. >350°; mixed m.p. with an authentic sample (m.p. >350°) >350°. The infrared spectra of the two materials were identical.

The benzene filtrate was washed with cold water, then with saturated aqueous salt solution, dried over sodium sulfate and evaporated *in vacuo*. A yellow oil (5.04 g., 81.5% yield) was obtained. It was dissolved in 100 ml. of ether, filtered and evaporated down to cloudiness. Seeding induced immediate crystallization; 3.91 g., m.p. 72–73°. A second crop amounted to 1.0 g. of the same m.p. (79.5% yield). This compound was identical with VII as obtained from XVII (mixed m.p., infrared spectrum).

Synthesis of the Lactol of γ-[3-(1-Methyl)-indolyl]-γ-ketopropylphosphonic Acid (XVIII).—A mixture of 1-[3′-(1′-methyl)-indolyl]-3-dimethylaminopropan-1-one hydrochloride (III)[10b] (1.7 g., 6.37 mmoles) and triethyl phosphite (10.6 g., 0.0637 mole) was heated at 180–195° for 65 minutes. The clear yellow solution was cooled, diluted with 150 ml. of benzene, washed once with water, twice with saturated aqueous salt solution, dried over sodium sulfate and evaporated on the steam-bath first under reduced pressure, then at 0.1 mm. A mixture of the crude diethyl phosphonate derivative (quantitative yield) and a solution of 3.6 g. of potassium hydroxide in 21 ml. of water was heated on the steam-bath with stirring for 8 hours. The clear brown solution was cooled and acidified with 10 ml. of concentrated hydrochloric acid. The resulting yellow oily solid was extracted thrice with chloroform. The chloroform solution was washed twice with saturated aqueous salt solution, dried over sodium sulfate and evaporated to a brown

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[11] The equivalent weight is based on the titration of the first replaceable hydrogen.

[12] Titration indicates the possible presence of a small amount of impurity (probably the dibasic acid), because a second inflection is observed which gives neut. equiv. 299.

[13] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 312.

oil (1.967 g.). Trituration with warm ethyl acetate gave a yellow solid, 1.059 g., m.p. 195–200°. Three recrystallizations from acetic acid afforded pale yellow prisms of XVIII, m.p. 207–209° (dec., discolors at 184°); infrared spectrum: bonded OH (2520, 2290); 6μ region: 1565, 1531, 1495; P=O (1236); P–O (995); *o*-disubstituted benzene (747); ultraviolet spectrum: λ_{max} 245 (14,200); 304 (14,200).

Anal. Calcd. for $C_{12}H_{14}NO_4P$: C, 53.93; H, 5.28; N, 5.24; P, 11.59. Found: C, 54.44; H, 5.72; N, 5.15; P, 11.26.

Condensation of I with Trimethyl Phosphite.—A mixture of I (35.8 g., 0.1 mole) and trimethyl phosphite (124 g., 1.0 mole) was heated for 3.5 hours at 153–163° (bath temperature). The reaction mixture, which contained a precipitate, was cooled, then diluted with 100 ml. of benzene and allowed to stand overnight. The precipitate was filtered and washed with benzene to give 17.64 g. (m.p. >350°, 88% yield) of tetramethylammonium iodide.

The yellow filtrate was evaporated *in vacuo* and the resulting oily residue was dissolved in chloroform, washed twice with water, then saturated salt solution and dried over sodium sulfate. The chloroform solution was evaporated at room temperature using a Rinco rotating vacuum type evaporator to give 21.6 g. (77%) of the dimethyl ester VIII.

A sample of the crude oil was crystallized from methanol–ether–petroleum ether (30–60°) in the cold (m.p. 120–123°) and then from benzene and once from benzene–ether; clusters of needles, m.p. 123.5–125°; ultraviolet spectrum: 241 (12,975); flex 256 (9,100); 298 (12,625); in 0.01 *N* alcoholic KOH: 242 (10,450); 263 (10,150); flex 273 (8,775); 298 (10,500); flex 332 (5,475); infrared spectrum: NH (3150); C=O (1625); C=C (1614, 1579, 1525, 1496); P=O (1250, 1242); P–O (1037; *o*-disubstituted benzene (749).

Anal. Calcd. for $C_{13}H_{16}NO_4P$: C, 55.51; H, 5.74; N, 4.98. Found: C, 55.64; H, 5.67; N, 4.75.

Hydrolysis of VIII to Methyl γ-(3-Indolyl)-γ-ketopropylphosphonate (XIII).—A mixture of crude II (19.7 g.), potassium hydroxide (19.6 g.) and 75 ml. of water was heated on the steam-bath with stirring for 4 hours. The solution was filtered, cooled and acidified with 33 ml. of concentrated hydrochloric acid. The resulting precipitate was filtered, washed with water and dried to give 14.4 g., melting at 126° (efferv.). Attempts to crystallize the material were unsuccessful.

The crude methyl ester XIII (0.6 g.) was treated with an excess of diazomethane in 50 ml. of ether and 30 ml. of methanol. The solution was evaporated to dryness and the yellow oily residue was crystallized from methanol–benzene–petroleum ether (30–60°) during 3 days to give 0.192 g. of the dimethyl ester VIII, melting at 120–122° (identity with the authentic sample was established by mixed m.p. and infrared comparison). The mother liquor was evaporated to give a yellow oil (0.372 g.). Quantitative infrared comparison of this oil with the pure dimethyl ester VIII in the NH region indicated 67.7% NH present, thus indicating that the crude methyl ester obtained from the alkaline hydrolysis contained 79% of XIII, the rest being accounted for, most likely, by the presence of the corresponding N-methylated compound.

The crude methyl ester XIII (0.5 g.) was dissolved in 3 ml. of hot acetic acid. Water (8 ml.) was added to the boiling solution and it was allowed to crystallize for 4 days. The crude product (0.4 g.) was purified by fractional crystallization from water to give a total of 0.2 g. of the pure phosphonic acid XIX melting at 205–207°. Identity with the sample of XIX, obtained from the isopropyl ester XIV (as described below) was established by mixed m.p. and infrared comparison.

Condensation of I with Triisopropyl Phosphite.—A mixture of I (35.8 g., 0.1 mole) and triisopropyl phosphite (208 g., 1 mole) was refluxed for 3.5 hours. The resulting suspension was cooled, diluted with 100 ml. of benzene and filtered. The precipitate (trimethylisopropylammonium iodide) weighed 5.38 g. and melted above 300°. After a few minutes, a colorless material started to crystallize in the filtrate. The crystals were filtered, washed with benzene and then with water to give 14.6 g. of diisopropyl γ-(3-indolyl)-γ-ketopropylphosphonate (IX), m.p. 128–129.5°.

The filtrate was evaporated *in vacuo* and the oily residue was dissolved in methylene chloride, washed with water, then with saturated salt solution and dried over sodium sulfate. The solution was evaporated at room temperature *in vacuo* to give an oily residue which crystallized overnight. Trituration with ether afforded 9.78 g. of IX, m.p. 127–128°. A further crop amounted to 3.96 g., melting at 126–130° (total yield 84%). A sample was recrystallized from benzene–petroleum ether (30–60°), colorless plates, m.p. 129–130°; ultraviolet spectrum: 241.5 (12,925); 256 (9,025) 302 (13,625); in 0.01 *N* KOH: 241 (10,500); 263 (10,150); flex 273 (8,800); 299 (10,500); 332 (5,400); infrared spectrum: NH (3100); C=O (1644); C=O (1619, 1580, 1524, 1499); P=O (1220); P–O (995); *o*-disubstituted benzene (739).

Anal. Calcd. for $C_{17}H_{24}NO_4P$: C, 60.52; H, 7.17; N, 4.15. Found: C, 60.89; H, 7.40; N, 4.17.

Alkaline Hydrolysis of IX to Isopropyl γ-(3-Indolyl)-γ-ketopropylphosphonate (XIV).—A mixture of IX (13.6 g.), potassium hydroxide (12.3 g.) and 110 ml. of water was heated on the steam-bath with stirring for 22 hours at which time some oil was still present. The mixture was cooled and extracted twice with ether. The ethereal extracts were worked up in the usual manner to give 0.54 g. of the unreacted IX, which melted at 127–129°, after crystallization from benzene–petroleum ether (30–60°).

The alkaline solution was cooled and acidified with 21 ml. of concentrated hydrochloric acid. The resulting precipitate was filtered, washed with water and dried to give 11.1 g. of XIV, m.p. 155–157° (efferv.). One gram of this material was dissolved in 950 ml. of acetone and the solution was evaporated down to *ca.* 100 ml. when crystallization commenced. Colorless plates of XIV were obtained, m.p. 173–174.5° (0.85 g.), unchanged on further recrystallization; ultraviolet spectrum: 210 (27,950); 241 (12,900); flex 256 (9,200); 297 (12,450); in 0.01 *N* KOH: 240 (12,275); flex 258 (9,225); 292 (12,000); flex 332 (895); infrared spectrum: NH (3180); P–OH (2640, 2320); C=O (1626); C=C (1580, 1557, 1523, 1511, 1492); P=O (1240); P–O (990); *o*-disubstituted benzene (754).

Anal. Calcd. for $C_{14}H_{18}NO_4P$: C, 56.95; H, 6.14; N, 4.74. Found: C, 57.19; H, 6.29; N, 4.73.

γ-(3-Indolyl)-γ-ketopropylphosphonic Acid (XIX).—Compound XIV (1.11 g.) was dissolved in 75 ml. of boiling water and 1 ml. of concentrated hydrochloric acid added. The solution was allowed to crystallize in the cold for 2 hours and filtered to give 0.9 g. of plates, m.p. 207.5–209.5° dec., unchanged on further recrystallization; ultraviolet spectrum: 209 (27,800); 241 (13,000); flex 256 (9,200); 295 (12,300); in 0.01 *N* KOH: 240.5 (12,600); 256 (9,760); 295 (12,250); broad flex 322 (737); infrared spectrum: NH (3240); P–OH (2700, 2340); C=O (1624); C=C (1580, 1513, 1493); P=O (1239); P–O (1073, 1002); *o*-disubstituted benzene (745).

Anal. Calcd. for $C_{11}H_{12}NO_4P$: C, 52.18; H, 4.78; N, 5.53. Found: C, 51.80; H, 4.67; N, 5.44.

Condensation of 1-3′-(5′-Benzyloxy)-indolyl-3-dimethylamino-1-propanone Hydrochloride (IV)[10b] with Trimethyl Phosphite.—A mixture of IV (25.16 g., 0.07 mole) and trimethyl phosphite (86.8 g., 0.7 mole) was heated for 3 hours at 155–158° (bath temperature). Two layers were formed. The excess of trimethyl phosphite was distilled *in vacuo*. The residue was cooled in ice and diluted with 100 ml. of benzene and 100 ml. of cold water, whereupon a thick colorless precipitate appeared. Methanol (25 ml.) was added to aid the filtration which afforded 16.23 g. of material. Crystallization from 80 ml. of methanol and 100 ml. of ether afforded needles, m.p. 146–146.5° (7.59 g.). The second crop amounted 4.56 g. of material melting at 141.5–142.5°. The yield of X based on these two crops was 45%. The analytical sample was prepared by recrystallization from methanol–ether, m.p. 147–148°; ultraviolet spectrum: 252 (18,500); flex 268 (11,300); 302 (11,000); in 0.01 *N* alcoholic KOH: 254 (14,500); 273 (12,400); flex 290 (9,750); flex 303 (9,750); infrared spectrum: NH (3170); C=O (1644); C=C (1625, 1589, 1526, 1489); P=O (1240); P–O (1054, 1030); aromatic (825, 797, 746, 740).

Anal. Calcd. for $C_{20}H_{22}NO_5P$: C, 62.01; H, 5.72; N, 3.61; P, 7.99. Found: C, 61.75; H, 5.33; N, 3.81; P, 8.03.

Hydrogenolysis of X to Dimethyl γ-[3-(5-Hydroxy)-indolyl]-γ-ketopropylphosphonate (XXI).—A suspension of X (1.94 g.) in 100 ml. of 95% ethanol was hydrogenated at 48 lb. of hydrogen pressure in the presence of 0.2 g. of 10% palladium-on-carbon. After 5 hours, 100 ml. of ethanol was added and the suspension of the product and the catalyst was filtered. The filtrate was evaporated to about 5 ml. when crystallization occurred to give 0.53 g. of XXI, melting at 223° dec. The catalyst mixture was treated with dimethylformamide at room temperature, filtered and the resulting solution diluted with ether to give a second crop of XXI (0.11 g., m.p. 224°), yield 43%. A sample was recrystallized for analysis from dimethylformamide–ether, m.p. 222° dec.; ultraviolet spectrum: 214 (28,200); 252 (17,000); 271 (11,200); 304 (11,550); in 0.01 *N* KOH: 218 (20,900); 249 (12,625); 256 (12,300); 290 (10,300); broad max. 344 (4,225); infrared spectrum: NH/OH (3200); C=O (1618); C=C (1587, 1529, 1496); P=O (1207); P-O (1067, 1049, 1027); aromatic (814, 806, 778, 752).

Anal. Calcd. for $C_{13}H_{16}NO_5P$: C, 52.53; H, 5.43; N, 4.71. Found: C, 52.91; H, 5.56; N, 4.99.

Hydrolysis of X to Methyl γ-[3-(5-Benzyloxy)-indolyl]-γ-ketopropylphosphonate (XV).—A mixture of X (13.22 g.) and 9.1 g. of potassium hydroxide in 35 ml. of water was heated on the steam-bath with stirring for 8 hours. The solution was cooled in ice and acidified with 26 ml. of concentrated hydrochloric acid whereupon an oily solid deposited. Chloroform (800 ml.) was added and the resulting insoluble precipitate was filtered, washed with chloroform and then with water; 11.21 g. (88% yield), m.p. 191–192.5°. Two crystallizations from dimethylformamide–ether afforded XV melting at 196.5–197.5°. A satisfactory analysis of this compound could not be obtained; ultraviolet spectrum: 214 (29,800); 252 (16,600); flex 268 (10,300); 300 (9,600); no change in alkali; infrared spectrum: NH (3200); P-OH (2740, 2460); C=O (1620); C=C (1585, 1514, 1480); P=O (1217); P-O (1045).

Treatment of XV with an excess of ethereal diazomethane solution afforded a quantitative yield of the dimethyl ester, m.p. 146–147°, which was identical with X (mixed m.p. and infrared). Treatment of XV with boiling acetic acid gave the phosphonic acid XX (m.p. 205–205.5°) which was identical with the sample prepared from the ethyl ester (XVI) (mixed m.p., infrared, ultraviolet and analyses) as described below.

Condensation of IV with Triethyl Phosphite.—A mixture of IV (30 g., 0.084 mole) and triethyl phosphite (140 g., 0.84 mole) was heated at 180–190° (bath temperature) for 2.75 hours. The cooled solution was diluted with 100 ml. of benzene and allowed to crystallize overnight. The precipitate XI was filtered and washed with benzene; 22.5 g., m.p. 166.5–167.5°. The filtrate was evaporated down (toward the end at 0.1 mm.) to a brown oily residue. It was dissolved in benzene, washed twice with water, then with saturated salt solution and dried over sodium sulfate. The residue obtained on evaporation was crystallized from ethanol and afforded a second crop of XI, m.p. 166.5–167.5°, 1.02 g. The third crop amounted to 0.5 g., m.p. 167–167.5°. The total yield was 69%. The analytical sample was obtained by recrystallization from ethanol; long needles, m.p. 169.5–170°; ultraviolet spectrum: 213.5 (34,800); 252 (19,075); flex 268 (11,625); 302 (11,300); in 0.01 *N* KOH: 213.5 (32,525); 252 (15,175); 272 (13,650); flex 288 (11,475); flex 304 (10,225); broad flex 328 (7,500); infrared spectrum: NH (3120); C=O (1642); C=C (1621, 1603, 1584, 1518, 1487, 1476); P=O (1221, 1205, 1199); P-O (1041, 1021); aromatic (791, 776, 740, 694).

Anal. Calcd. for $C_{22}H_{26}NO_5P$: C, 63.60; H, 6.31; N, 3.37; P, 7.45. Found: C, 63.91; H, 6.63; N, 3.64; P, 6.98.

Hydrolysis of XI to Ethyl γ-[3-(5-Benzyloxy)-indolyl]-γ-ketopropylphosphonate (XVI).—A mixture of XI (15 g.) and potassium hydroxide (10.1 g.) in 87 ml. of water was heated on the steam-bath with stirring for 8 hours. It was then cooled in ice and acidified with 20 ml. of concentrated hydrochloric acid. The resulting colorless precipitate was filtered and washed well with water, 14.0 g., m.p. 170–179° (titration indicated that a second component, probably the dibasic acid, is present to the extent of about 10%). Crystallization from ethanol afforded pale yellow clusters of XVI, m.p. 173.5–175°; ultraviolet spectrum: 214 (33,675); 252 (18,825); 268 (11,500); 300 (10,950); no change in alkali; infrared spectrum: NH (3170); P-OH (2600, 2260); C=O (1625); C=C (1614, 1587, 1516, 1482); P=O (1266); P-O (1152, 1125, 1045).

Anal. Calcd. for $C_{20}H_{22}NO_5P$: C, 62.01; H, 5.72; N, 3.62. Found: C, 61.53; H, 5.64; N, 3.72.

γ-[3-(5-Benzyloxy)-indolyl]-γ-ketopropylphosphonic Acid (XX).—The ethyl ester XVI (0.5 g.) was dissolved in 5 ml. of hot acetic acid. Shortly after a solution was obtained, precipitation of a colorless product occurred while the mixture was still at reflux. The product XX was filtered and washed with ether, 0.45 g., m.p. 210–211° (fast). Crystallization from 90 ml. of acetic acid afforded pink plates, m.p. 206–207.5°; ultraviolet spectrum: 214 (32,700); 252 (18,000); flex 268 (11,000); 301 (10,500); no change in alkali; infrared spectrum: NH (3210); P-OH (2700, 2340); C=O (1616); C=C (1586, 1612); P=O (1245); P-O (1090, 1080, 1000); aromatic (796, 736).

Anal. Calcd. for $C_{18}H_{18}NO_5$: C, 60.17; H, 5.05; N, 3.90. Found: C, 59.89; H, 4.96; N, 3.68.

Treatment of XX (0.5 g.) with an excess of diazomethane in ether–methanol solution afforded 0.45 g. of the dimethyl ester X which melted at 147.5–148° after crystallization from ether (mixed m.p. with the authentic sample showed no depression).

Lactol of γ-[3-(1-Ethyl-5-benzyloxy)-indolyl]-γ-ketopropylphosphonic Acid (XXIII).—The ethyl ester XVI (3.87 g., 0.01 mole) was dissolved in 47 ml. of 10% aqueous sodium hydroxide and 6.5 ml. (0.05 mole) of diethyl sulfate was added dropwise while the mixture was stirred and heated on the steam-bath. When the exothermic reaction subsided, 37 ml. of 10% sodium hydroxide was added followed by 6.5 ml. of diethyl sulfate and this process was repeated once more. The reaction mixture was then heated for 1.5 hours. The clear, yellow alkaline solution was cooled and acidified with 20 ml. of concentrated hydrochloric acid. The resulting oily material was extracted three times with chloroform. The combined chloroform extracts were washed with water, then twice with saturated salt solution and evaporated at room temperature *in vacuo* to give 4.0 g. of a yellow oil. The infrared spectrum showed no NH; P-OH (2600, 2270); C=O (1642); C=C (1620, 1580, 1527, 1500); P=O (1212) and P-O (1035, 989, 950) and was compatible with the structure of ethyl γ-[3-(1-ethyl-5-benzyloxy)-indolyl]-γ-ketopropylphosphonate (XXII).

The above crude oil (3.7 g.) was dissolved in boiling acetic acid (10 ml.) and allowed to crystallize; 1.2 g., m.p. 190–192.5° (s. 188°). The filtrate was diluted with ether and deposited a second crop of 0.4 g., m.p. 190–192°. On standing for a period of about a week, the filtrate deposited three further crops which amounted to 1.4 g., m.p. 190–194° (total yield 81%). A sample of XXIII was recrystallized from acetic acid; colorless clusters, m.p. 190–191.5°; ultraviolet spectrum: 217 (31,150); 256 (19,925); 305 (11,900); no change in alkali; infrared spectrum: bonded OH and P-OH (2500, 2140); C=O absent; C=C (1622 vw, 1590, 1535, 1485); P=O (1274, 1225); P-O (990); aromatic (796, 739, 716).

Anal. Calcd. for $C_{20}H_{22}NO_5P$: C, 62.01; H, 5.73; N, 3.62. Found: C, 62.14; H, 5.87; N, 3.58.

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