3-Methylorotic acid (XIII). 2-Amino-3-methyl-4-oxo-3,4-dihydropyrimidine-6-carboxylic acid (100 mg., 0.59 mmole) (XII) was dissolved in 2 ml. of 1*N* sodium hydroxide and heated for 1.5 hr. on a steam bath during which time the volume decreased to 1 ml. The volume was adjusted to 2 ml. with water and the solution acidified to *p*H 5 with glacial acetic acid; yield 12 mg. Paper chromatography in solvent E showed this crop to be a mixture of starting material (R_f 0.54) and an unidentified, lower R_f product. The filtrate was further acidified with 6*N* hydrochloric acid to give 34 mg. (34%) of 3-methylorotic acid m.p. 313–316°. This was identical (melting point and chromatography in solvent E [R_f 0.66)] to an authentic specimen prepared by the method of Fox *et al.*[17]

Decarboxylation of 2-amino-3-methyl-4-oxo-3,4-dihydropyrimidine-6-carboxylic acid (XII). Compound XII (0.75 g., 4.4 mmoles) was refluxed for 2 hr. in 100 ml. of quinoline. The quinoline solution was then extracted with three 100-ml. portions of water and the combined water washings were extracted with ether (to remove excess quinoline). The aqueous layer was evaporated to dryness *in vacuo* and the residue was taken up in about 50 ml. of absolute alcohol. After concentrating the solution to about 15–20 ml. and chilling there was obtained 137 mg. of product. Two further crops weighing 82 and 42 mg. (47%) total yield) were obtained by concentrating the mother liquor. All three crops traveled side-by-side with 3-methylisocytosine in solvents A (R_f 0.62) and E (R_f 0.77). The three crops were combined and recrystallized from 8 ml. of ethanol using Norit; yield 100 mg., m.p. 264–267°. The infrared spectrum of this product was identical with the spectrum of the 3-methylisocytosine obtained by methylation.

Acknowledgment. The authors are indebted to Mr. William Fulmor and staff for the spectral data, Mr. Louis Brancone and staff for the microanalytical data, and Mr. Charles Pidacks and staff for the chromatographic separations.

PEARL RIVER, N. Y.

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[17] J. J. Fox, N. Yung, and I. Wempen, *Biochim. et Biophys. Acta*, 23, 295 (1957).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, AUBURN UNIVERSITY]

Synthesis of Some Pyrimidylphosphonates

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Nine dialkyl pyrimidylphosphonates and six free phosphonic acids, corresponding to these esters, were synthesized for biological studies by modifications of the Arbuzov and the Michaelis reactions.

The present investigation was undertaken for the purpose of exploring the possibilities of biological activity among organophosphorus compounds containing a pyrimidyl radical joined directly to a phosphorus atom. Our particular attention was directed to the compounds of the phosphonic acid family, *i.e.*, $RPO(OH)_2$, in which the radical is a pyrimidyl group either with the most simple substituents or one that is unsubstituted otherwise. This selection was made in order that the behavior of the simplest members of the series could be evaluated. This line of approach appeared to be potentially useful in view of the existence of many biologically important organic compounds which contain the pyrimidyl radical in one form or another. The compounds constituted about a pyrimidyl radical joined directly to phosphorus could constitute a possible line of metabolic antagonists since it might be expected that the carbon-phosphorus bond would prove to be resistant to enzymatic cleavage and the substantially dipolar molecules could be expected to persist in a living cell.

It was shown by one of us some years ago that the conventional Arbuzov and Michaelis reactions may be applicable for the synthesis of phosphonates from nitrogen heterocycles containing a halogen atom at a carbon atom in the cycle.[2] For this reason, this specific approach was used for the synthesis of various pyrimidyl members. The very low reactivity of 5-halopyrimidine prevented the synthesis of the 5-pyrimidylphosphonate, but the analogous 2- and 4-isomers were prepared successfully, as were seven phosphonates with various substituents in the pyrimidine cycle.

It may be noted that several unsuccessful attempts to accomplish such syntheses may be found in the earlier literature.[3]

The phosphonates synthesized by us displayed a strong absorption band at 300–320 mμ in the ultraviolet. The infrared absorption spectra of these substances were also examined. The notable features of these spectra are as follows. The 2-pyrimidylphosphonate displays a sharp peak at 1225 cm.$^{-1}$ which is absent in the spectrum of the 4-isomer. The 2-chloro-4-pyrimidylphosphonate shows a band at 685 cm.$^{-1}$, probably caused by the C—Cl grouping, as this band does not appear in the substances devoid of chlorine in the 2-position. The normally expected absorption near 990 cm.$^{-1}$ for the pyrimidine ring is obscured by the prox-

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[1] This material represents the dissertation submitted by C. H. Roy in partial fulfillment of the requirements for the Ph.D. degree at the Auburn University School of Graduate Studies in June 1960.

[2] G. M. Kosolapoff, *J. Am. Chem. Soc.*, 69, 1002 (1947).

[3] B. A. Arbuzov and B. P. Lugovkin, *Zhur. Obshchei Khim.*, 22, 1199 (1952); A. Burger, J. B. Clements, N. D. Dawson, and R. B. Henderson, *J. Org. Chem.*, 20, 1383 (1955).

imity of the phosphorus ester group absorption in that region, but the spectrum of the 4,6-dimethyl-2-pyrimidylphosphonate shows the pyrimidine absorption satisfactorily owing to the bathochromic shift of the phosphorus absorption band.

On the basis of the preliminary biological evaluation of the compounds in this group, we must report, with some regret, that the substances are biologically inactive, expectations to the contrary notwithstanding. Only the esters of 2-amino- and 2-chloro-4-pyrimidylphosphonates displayed a biological activity, in the sense of being quite toxic to experimental animals.

EXPERIMENTAL

Diethyl 4,6-dimethyl-2-pyrimidylphosphonate. The necessary 4,6-dimethyl-2-hydroxypyrimidine was prepared by a modification of the method described by Evans[4]: 60.1 g. of urea in 500 ml. of boiling absolute ethanol was treated with 100 g. of 2,4-pentanedione and the hot solution was treated with 135 ml. of concd. hydrochloric acid with stirring. The reaction became exothermic after some 5 min. and required moderation by cooling. The mixture was kept for 24 hr., after which 71% of 4,6-dimethyl-2-hydroxypyrimidine hydrochloride was isolated by filtration.

The conversion of this material to the 2-chloro analog was performed by a modification of the procedure described by Angerstein[5]: 1 pound of phosphorus oxychloride was refluxed for 10 hr. with 82.2 g. of the above hydrochloride, after which the residual phosphorus oxychloride was removed *in vacuo.* The residual liquid was quenched in 200 g. of ice and neutralized with concentrated potassium hydroxide solution at below 10°. The resulting mixture was continuously extracted with ether for 24 hr. and the extract was distilled, yielding 62.4 g. (85.5%) of 4,6-dimethyl-2-chloropyrimidine, boiling at 210–212°; m.p. 38–39°.

This material (42.3 g.), in toluene solution, was added over 30 min. to the solution of diethyl sodium phosphite, prepared from 13.8 g. of sodium in 1.5 l. of toluene. The reaction mixture began to deposit sodium chloride during this addition and, after a brief period, the remaining 31.7 g. of the chloropyrimidine was added. The mixture was refluxed with stirring for 9 hr. longer. The liquid phase was decanted phase was decanted from the agglomerated solid and the latter was extracted with two portions (100 ml.) of toluene and one portion of ether, after addition of 300 ml. of water. The combined organic solution was freed of the solvents in *vacuo;* the residue was suspended in 300 ml. of water and extracted with 1 l. of chloroform. The extract was distilled, yielding 35.5 g. (27.8%) of diethyl 4,6-dimethyl-2-pyrimidylphosphonate, as a colorless liquid, boiling at 121–122° at 0.07 mm.; n_D^{25} 1.4880; n_D^{30} 1.4847; d_4^{30} 1.1298.

Anal. Calcd. for $C_{10}H_{17}O_3N_2P$: P, 12.68; N, 11.47. Found: P 12.65; N 11.25.

Treatment of the ester with dry hydrogen bromide at approximately 80° for several hours and recrystallization of the residue from acetone-ethyl acetate, with good protection from atmospheric moisture, yielded the extremely hygroscopic 4,6-dimethyl-2-pyrimidylphosphonic acid, which sublimed readily at above 100° and melted at 153–154°. The hygroscopic nature of this acid prevented a satisfactory elemental analysis of the acid, but the nature of the substance was confirmed by an electrometric titration curve.

Diisopropyl 2-pyrimidylphosphonate. The necessary 2-chloropyrimidine was prepared, with some modifications of the published procedures, as follows. For the synthesis of 2,4-dichloropyrimidine,[6] 100 g. of uracil was refluxed with stirring for 3.5 hr. with 400 ml. of phosphorus oxychloride (the shortened reaction period served to reduce the formation of tarry products), after which the mixture was freed of excess oxychloride *in vacuo* at 50°, and the residue was quenched in ice and extracted with chloroform. The extract, washed with dilute sodium carbonate and dried, yielded 97.3 g. (72.3%) of 2,4-dichloropyrimidine, melting at 60–61°. The same material was prepared according to Johnson[7] from thiouracil and phosphorus pentachloride-oxychloride mixture. However, the yield of the final product in this case was but 44.4%.

Reduction of 2,4-dichloropyrimidine was performed by a modification of the procedure described by Boarland *et al.*,[8] which gave a substantial improvement in the yield (from 28.8% to 68%). A solution of 13.2 g. of ammonium chloride in water was refluxed with vigorous stirring with 51 g. of 2,4-dichloropyrimidine and 66.6 g. of zinc dust until the refluxing material in the condenser just became homogeneous (about 45 min.), the mixture was cooled to about 70°, filtered from the solids, which were washed with a little acetone and several portions of chloroform, and the total filtrate was extracted eight times with 100-ml. portions of chloroform. After evaporation of the solvent in vacuum and sublimation of the residue under reduced pressure, there was isolated 22.9 g. (68%) of 2-chloropyrimidine, melting at 64–65°.

This (22.9 g.) was refluxed for 13 hr. with 83.3 g. of triisopropyl phosphite, the evolving isopropyl chloride being collected in a chilled trap. The residual material in the reaction flask was distilled and yielded 34.8 g. (71.5%) of diisopropyl 2-pyrimidylphosphonate, boiling at 125–126° at 0.03 mm. The product crystallized on standing and, after two recrystallizations from ether–petroleum ether (b.p. 30–50°), melted at 59.5–61°. The unrecrystallized product was not very stable and gradually decomposed during storage. The recrystallized material appeared to be completely stable.

Anal. Calcd. for $C_{10}H_{17}O_3N_2P$: P, 12.68; N, 11.47. Found: P, 12.83; N, 11.38.

Passage of dry hydrogen bromide into a solution of the ester in refluxing toluene for 7 hr. and crystallization of the product from isopropyl alcohol yielded some 40% of free 2-pyrimidylphosphonic acid, in the form of yellowish needles, melting at 212–214°.

Anal. Calcd. for $C_4H_5O_3N_2P$: P, 19.35; N, 17.65. Found: P 19.20; N 17.65.

Diisopropyl 2-chloro-4-pyrimidylphosphonate. The reaction was run as described above with 94.2 g. of 2,4-dichloropyrimidine and 165 g. of triisopropyl phosphite, the mixture being heated rapidly to 160° and kept at 165–175° for 20 min., during which period 42.4 g. of isopropyl chloride was collected (theoretical amount—42.2 g.). The residue was distilled rapidly and about 50 ml. of low-boiling material was collected up to 123° at 0.1 mm. Further distillation gave 113.1 g. (64.8%) of diisopropyl 2-chloro-4-pyrimidylphosphonate, which was collected at 123–127° at 0.1 mm. At this time the residue began to decompose rather vigorously and the distillation was terminated after the collection of approximately 10 g. of additional product. The total yield was 123 g. or 70.5%. A redistillation gave the pure product, boiling at 125.5–126.5° at 0.15 mm.; n_D^{25} 1.4817; d_D^{25} 1.1860.

Anal. Calcd. for $C_{10}H_{16}O_3ClN_2P$: P, 11.11; N, 10.05. Found: P 11.09; N 9.82.

This ester was found to be quite sensitive to heat and each redistillation resulted in much loss, caused by resinification and decomposition of the residue. At times this de-

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(4) P. N. Evans, *J. prakt. Chem.*, **48**, 489 (1893).

(5) St. Angerstein, *Ber.*, **34**, 3956 (1901).

(6) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 1152 (1930); J. D. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).

(7) T. B. Johnson and G. A. Menge, *J. Biol. Chem.* **2**, 105 (1906).

(8) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951).

composition was very violent. In a reaction of the same components, but employing a double proportion of the phosphite, the reaction ended in a nearly explosive decomposition of the mixture after some 75% of the theoretical volume of isopropyl chloride had been collected. The resinous residue after this decomposition contained 2.65% of phosphorus. It was not examined further. This reaction was run in an endeavor to form the corresponding pyrimidine-2,4-diphosphonate.

Treatment of the diisopropyl ester with hydrogen bromide in hot toluene gave the free 2-chloro-4-pyrimidylphosphonic acid, in the form of a very hygroscopic solid, which decomposed at 157–160°.

Diisopropyl 2-amino-4-pyrimidylphosphonate. A refluxing solution of 60 g. of diisopropyl 2-chloro-4-pyrimidylphosphonate in 50 ml. of toluene was treated with dry ammonia. The reaction was rather exothermic initially and heating was temporarily suspended. After this, the mixture was refluxed in a stream of ammonia for 12 hr. The cooled mixture was filtered and the solids were washed with hot isopropyl alcohol. The residue of ammonium chloride weighed 10.22 g. (theoretical weight 11.5 g.). The filtrates were evaporated under reduced pressure and the residual oil was taken up in hot isopropyl alcohol (200 ml.). The filtered solution was gradually evaporated under reduced pressure until crystallization began, after which it was chilled, whereupon the product crystallized. After four recrystallizations from 1:1 aqueous isopropyl alcohol, there was isolated 27.6 g. (49.6%) of diisopropyl 2-amino-4-pyrimidylphosphonate, which melted at 163–165°.

Anal. Calcd. for $C_{10}H_{18}O_3N_3P$: P, 11.95; N, 16.21. Found: P 11.62; N 16.04.

A similar reaction in an aqueous medium gave a yield of 30.6%. The ester treated with hydrogen bromide, as described previously, gave the free acid which was a very hygroscopic solid, subliming at 250° and not melting above 300°.

Diisopropyl 2-dimethylamino-4-pyrimidylphosphonate. Reaction mixture of 28.1 g. of diisopropyl 2-chloro-4-pyrimidylphosphonate was treated slowly with dimethylamine (the reaction is very vigorous at first) taken in large excess in an apparatus provided with a Dry Ice-cooled reflux condenser. After 15 min. at room temperature, the excess amine was allowed to evaporate, the residue was taken up in ethyl ether and the extract was washed with three 10-ml. portions of cold water, two 10-ml. portions of dilute sodium carbonate, and two more 10-ml. portions of water (the washing is essential for the isolation of the product). The dried solution was distilled, yielding 18.7 g. (65.1%) of diisopropyl 2-dimethylamino-4-pyrimidylphosphonate, which boiled at 110–112° at 0.05 mm. The product solidified readily and melted at 28–29°. The product boils at 98–100° at 0.03 mm. and in supercooled state has n_D^{25} 1.5005, d_4^{25} 1.1006.

Anal. Calcd. for $C_{12}H_{22}O_3N_3P$: P, 10.78; N, 15.10. Found: P, 10.85; N, 14.87.

Treatment of the ester with hydrogen bromide, as described above, gave the free phosphonic acid, which formed a hygroscopic powder, melting at 196–198°.

Diisopropyl 2-diethylamino-4-pyrimidylphosphonate. A reaction of 17.3 g. of diisopropyl 2-chloro-4-pyrimidylphosphonate with 25 ml. of diethylamine (vigorous at first) was completed by 2 hr. at room temperature and 10 min. of refluxing. The mixture yielded 17.8 g. (91%) of diisopropyl 2-diethylamino-4-pyrimidylphosphonate, a colorless liquid, boiling at 113–114° at 0.05 mm., n_D^{25} 1.4943, d_4^{25} 1.0670.

Anal. Calcd. for $C_{14}H_{26}O_3N_3P$: P, 9.82; N, 13.19. Found: P, 9.82; N, 13.19.

Diisopropyl ester described above yielded a deliquescent, amorphous mass in attempts to convert it to the free acid.

Diisopropyl 2-ethoxy-4-pyrimidylphosphonate. A mixture of 13.9 g. of diisopropyl 2-chloro-4-pyrimidylphosphonate, 75 ml. of absolute ethanol, and 3 g. of Raney nickel catalyst W5[9] was hydrogenated under 45 p.s.i. hydrogen pressure in the presence of 2.8 g. of potassium hydroxide in absolute ethanol. After 9 hr. only a minor drop in hydrogen pressure was observed in the Parr hydrogenation apparatus. The solution was filtered, evaporated, taken up in dry ethyl ether, washed with water to remove any chloride ions, and distilled after drying. There was obtained 5.8 g. (59.2%) of diisopropyl 2-ethoxy-4-pyrimidylphosphonate, boiling at 120–122° at 0.05 mm.; n_D^{29} 1.4753, n_D^{25} 1.4764, d_D^{29} 1.1090.

Anal. Calcd. for $C_{12}H_{21}O_4N_2P$: N, 9.72; P, 10.74. Found: N, 9.72; P, 10.74.

Diisopropyl 4-pyrimidylphosphonate. Hydrogenation of 27.9 g. of diisopropyl 2-chloro-4-pyrimidylphosphonate in the presence of 4.8 g. of magnesium oxide and 10.3 g. of 5% palladium on carbon catalyst in 375 ml. of 1:2 aqueous methanol with vigorous stirring at normal pressure and temperature for 8 hr., resulted in the calculated volume of absorbed hydrogen. The mixture was filtered, the filtrate evaporated under reduced pressure, suspended in 200 ml. of water, and thoroughly extracted with five 100-ml. portions of ethyl ether. Evaporation of the solvent yielded the crude product (16.9 g.; 69.2%), which crystallized readily. This material was distilled yielding the pure product which boiled at 91–92° at 0.015 mm. and solidified on cooling to colorless solid, melting at 30.5–31.0°.

Anal. Calcd. for $C_{10}H_{17}O_3N_2P$: N, 11.47; P, 12.68. Found: N, 11.19; P, 12.68.

Attempted preparation of the free phosphonic acid by hydrolysis of the ester with aqueous hydrochloric acid failed. However, the use of dry hydrogen bromide, described above, gave the free 4-pyrimidylphosphonic acid as a very hygroscopic solid which does not melt above 300°.

Attempted synthesis of diethyl 2,4-dihydroxy-5-pyrimidylphosphonate. A modification of Hilbert's method[10] was used to prepare 5-bromouracil. Uracil, 100 g., in 400 ml. of water was treated with 60 ml. of bromine (the additional 40 ml. of bromine recommended in the above reference was found to be unnecessary and even undesirable). As the solution was allowed to cool to 30°, the product crystallized and was separated. This was washed with 100 ml. of water, 100 ml. of absolute ethanol, and 100 ml. of ethyl ether. The washed product was dried at 115°, yielding 121.5 g. (71.2%) of 5-bromouracil, melting at 312–313°. This material failed to react with triethyl or triisopropyl phosphites. A reaction of 0.1 mole of 5-bromouracil with 0.2 mole of diethyl sodium phosphite in 40 ml. of absolute ethanol gave a gel after having been refluxing for 2.25 hr. with stirring. The mixture was filtered with some difficulty and the solid was found to contain much ionic bromine, indicating a considerable degree of removal of the halogen atom from bromouracil. The filtrate gave a mixture of products which contained the pyrimidine ring, as indicated by their ultraviolet absorption spectra. However, these materials did not contain any organic phosphorus.

Similarly unsuccessful was a ring closure, patterned after Johnson.[11] A mixture of 44.8 g. of triethyl phosphonoacetate and 16.3 g. of ethyl formate was added dropwise to 4.6 g. of sodium suspended in 100 ml. of ethyl ether. The mixture was stirred for 12 hr., yielding a difficulty stirrable suspension of the sodium salt of formylphosphonoacetate. This mixture was treated with 18 g. of urea after which the suspension became much more fluid. The whole was refluxed for 2 hr. The liquid portion was separated from the solid, but evaporation of the former at room temperature left no appreciable residue. Recrystallization of the solid from various solvents gave a series of solid substances, most of which absorbed strongly at 270 mμ, but none of these could be purified satisfactorily.

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(9) G. W. Kenner, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948); S. E. Krahler and A. Burger, *J. Am. Chem. Soc.*, **63**, 2367 (1941).

(10) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **56**, 134 (1934).

(11) T. B. Johnson and J. C. Ambelang, *J. Am. Chem. Soc.*, **60**, 2941 (1938).

Dibutyl 2-methyl-5-pyrimidylphosphonate. A warm solution of 6.9 g. of sodium in 115 ml. of absolute ethanol was prepared and 72 ml. of this was added, with stirring, to 18 g. of acetamidine hydrochloride in 20 ml. of absolute ethanol, after which a solution of 20.6 g. of mucobromic acid in 35 ml. of absolute ethanol was added gradually, the mixture being kept at 50–55°, which temperature range is the optimum for this reaction. When the reaction within the mixture began to subside, the remaining sodium ethoxide solution was added over 2 min. and the dark brown solution was stirred for 24 hr. at room temperature. The solids were filtered off and the filtrate, after having been evaporated *in vacuo*, was treated with 50 ml. of $2N$ hydrochloric acid and shaken vigorously, yielding 17.4 g. (57.5%) of 2-methyl-5-bromo-4-pyrimidinecarboxylic acid, which decomposed at 170–172°.[12] This acid was decarboxylated thermally and yielded 86.5% of 2-methyl-5-bromouracil, which melted at 83–84°.[12] A reaction of 6.37 g. of this substance in refluxing toluene with dibutyl sodium phosphite, prepared from 0.85 g. of sodium and 7.15 g. of dibutyl hydrogen phosphite, gave a considerable precipitate of sodium bromide after the mixture had been refluxed for 6 hr. The mixture was filtered and the filtrate evaporated *in vacuo*. However, the distillation of residual material yielded only some dibutyl butylphosphonate and tar. However, a reaction of 9.25 g. of 2-methyl-5-bromopyrimidine with butyllithium, prepared from 1.11 g. of lithium and 8.7 g. of butyl bromide in ethyl ether at −40°, followed by the addition, after 7 min., of 13.7 g. of dibutyl phosphorochloridate over 5 min., gave a moderate precipitate in the reaction mixture. The whole was allowed to warm up to −20° over 5 min. and to 0° over 10 min. After the temperature had risen to 20°, a brownish precipitate began to form and the mixture was stirred for 16 hr., after which the reaction appeared to be complete. The filtered solution was washed with dilute hydrochloric acid and sodium carbonate, after which it was dried and distilled, yielding three fractions: (1) b.p. of 100–130° at 0.05 mm., n_D^{25} 1.4347 (1.54 g.), (2) b.p. of 130–134° at 0.05 mm., n_D^{25} 1.4552 (1.2 g.), and (3) b.p. of 134° at 0.05 mm., n_D^{25} 1.4538 (0.9 g.). Fraction (1) was almost nitrogen-free. The other fractions were combined and chilled for several hours, yielding a small amount of a solid, which melted at 134°; this solid was devoid of phosphorus. The filtrate from this solid was adsorbed on a column of aluminum oxide and was eluted with 1:1 benzene–petroleum ether mixture. The first eluate was free of nitrogen, but the following fractions yielded a very small amount of a light yellow liquid, which boiled at 134° at 0.05 mm.; n_D^{25} 1.4540. This appeared to be the desired dibutyl 2-methyl-5-pyrimidylphosphonate, which showed the expected pyrimidine absorption in the ultraviolet. The product was not pure, but the very low yield of it prevented a further purification.

Anal. Calcd.: P, 10.51; N, 9.89. Found: P, 10.51; N, 9.48.

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AUBURN, ALA.

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[12] Z. Budesinsky, *Collection of Czechoslov. Chem. Commun.*, 14, 223 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

2-Amino-3(2H)isoquinolone, 2,3-Benzodiazepin-4(5H)one, and Related Compounds

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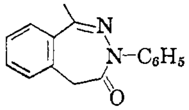
Two isomeric dehydration products of *o*-acetylphenylacetic acid phenylhydrazone are characterized by their hydrolysis products and spectra as 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)-one and 1-methyl-2-(phenylamino)-3(2H)isoquinolone. Additional benzodiazepinones and *N*-aminoisoquinolones obtained from the *o*-acetylphenylacetic acid semicarbazone and from the phenylhydrazone and semicarbazone of *o*-formylphenylacetic acid are described. The structure assignment is supported by the easy acid hydrolysis of 1-methyl-2-amino-3(2H)isoquinolone to *o*-acetylphenylacetic acid hydrazone hydrochloride. Methyl *o*-acetylphenylacetate, *o*-acetylphenylacetic acid methylphenylhydrazone, *o*-acetylphenylacetic acid azine, *o*-acetylphenyldimethylacetic acid, and *o*-acetylphenyldimethylacetic acid phenylhydrazone phenylhydrazide have been synthesized.

The elimination of one molecule of water from *o*-acetylphenylacetic acid phenylhydrazone[1] yields two isomeric products, one colorless, the other bright yellow. Pyrolytic dehydration at 190° produces principally the colorless product, while warming in a $1M$ solution of sulfuric acid in acetic acid gives the yellow isomer as the main product.

Upon treatment with sodium hydroxide in boiling ethylene glycol and subsequent acidification, the colorless isomer reverts to *o*-acetylphenylacetic acid phenylhydrazone. With hot concentrated hydrochloric acid, the yellow isomer is converted to *o*-acetylphenylacetic acid. These observations limit the acceptable structures for the colorless compound to I (1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)one) and II (1-methyl-2-(phenylamino)-3(2H)isoquinolone). It is most probable that the yellow compound is the other of these two structures. As no procedure has been found which will remove the nitrogen atoms one at a time from these compounds, and as the absorption of the



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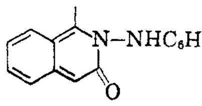

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[1] J. O. Halford and B. Weissmann, *J. Org. Chem.* 18, 30 (1953).