Deoxygenations of Isocyanates and Diphenylketene by Tertiary Phosphites

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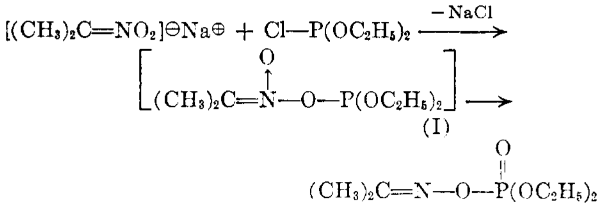
Deoxygenations of diphenylfuroxane, azoxybenzene, isocyanates, ethyl isothiocyanate, and diphenylketene have been studied. When diphenylfuroxane or azoxybenzene was treated with triethyl phosphite, diphenylfurazan or azobenzene was obtained in excellent yield along with triethyl phosphate. Further, when isocyanates and ethyl isothiocyanate were treated with tertiary phosphites, the corresponding isonitriles were obtained in fairly good yields. On the other hand, an addition compound was obtained from the reaction of diphenylketene and triethyl phosphite. The pyrolysis of the adduct led to the formation of diphenylacetylene, the deoxygenated product, and triethyl phosphate along with the dimer of diphenylketene.

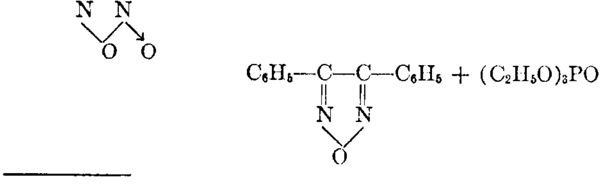
It is well known that amine oxides,[1] azoxybenzene, and substituted nitrosobenzenes[2] are deoxygenated by means of tertiary phosphines. However, there are few reports dealing with deoxygenation reactions by means of tertiary phosphites except in the cases of ethylene oxides,[3] phthalic anhydride,[4] and pyridine 1-oxide,[5] which are reduced to ethylene, biphthalyl, and pyridine, respectively.

On the other hand, it has been recently found[6] that the sodium salt of 2-nitropropane reacts with diethyl phosphorochloridite to form diethyl isopropylideneaminophosphate. The reaction can be explained by assuming intramolecular deoxygenation by means of the trivalent phosphorus of the nitronic ester (I) to yield a pentavalent phosphorus in the oximinophosphate.

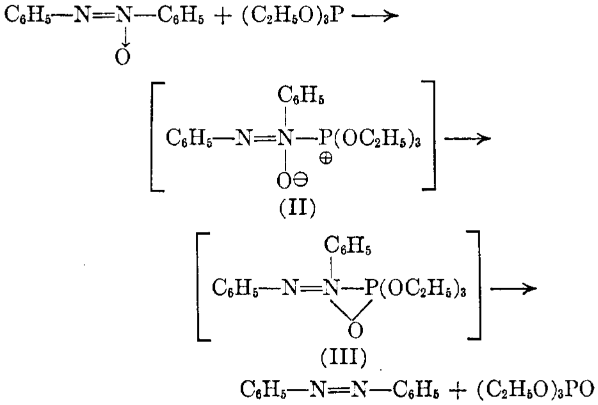


$$[(CH_3)_2C{=}NO_2]^{\ominus}Na^{\oplus} + Cl{-}P(OC_2H_5)_2 \xrightarrow{-NaCl} \underset{(I)}{\left[(CH_3)_2C{=}\overset{O}{\overset{\uparrow}{N}}{-}O{-}P(OC_2H_5)_2\right]} \longrightarrow (CH_3)_2C{=}N{-}O{-}\overset{O}{\overset{\|}{P}}(OC_2H_5)_2$$

In the present study, it was found that the reaction of triethyl phosphite with diphenylfuroxane resulted in the formation of diphenylfurazan and triethyl phosphate; when diphenylfuroxane was treated with triethyl phosphite at 160–170° for five hours under nitrogen, diphenylfurazan and triethyl phosphate were obtained in 93% and 94% yields, respectively.

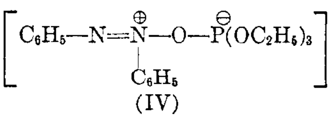


Similarly, azoxybenzene was deoxygenated by triethyl phosphite to form azobenzene in 91% yield.



As shown in the above scheme, a dipole structure (II), which is initially formed by the nucleophilic attack of the phosphorus on the positively charged nitrogen, is considered to be a necessary intermediate for these deoxygenation reactions. A similar attack by the negatively charged oxygen on the phosphorus results in the formation of a quasi three-membered ring intermediate (III). The subsequent cleavage of both the nitrogen–phosphorus and the nitrogen–oxygen bonds results in the formation of the phosphate and the reduced product.

There is an alternative pathway of deoxygenation *via* an intermediate (IV), which is formed by the coördination of the oxygen to the phosphite.



$$\left[C_6H_5{-}N{=}\overset{\oplus}{\underset{C_6H_5}{N}}{-}O{-}\overset{\ominus}{P}(OC_2H_5)_3\right]$$

(IV)

This type of reaction was next extended to isocyanate compounds on the assumption that isonitriles could be formed by deoxygenation with triethyl phosphite through a similar dipole structure (V) or coördinated structure (VI).

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(1) E. Howard, Jr., and W. F. Olszewski, *J. Am. Chem. Soc.*, **81**, 1483 (1959).

(2) L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, 473 (1956).

(3) C. B. Scott, *J. Org. Chem.*, **22**, 1118 (1957).

(4) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Am. Chem. Soc.*, **83**, 173 (1961).

(5) M. Hamana, *J. Pharm. Soc. Japan*, **75**, 121 (1955).

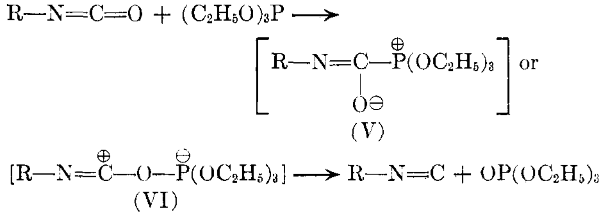
(6) T. Mukaiyama and H. Nambu, *J. Org. Chem.*, **27**, 2201 (1962).

TABLE I

REACTIONS OF ISOCYANATES WITH TRIETHYL PHOSPHITE

	Reaction		Yield, %			Recovered, %	
Isocyanate	Temp.	Time, hr.	R—NC	R—CN	$(C_2H_5O)_3PO$	R—NCO	$(C_2H_5O)_3P$
Ethyl	180° (in a sealed tube)	11	34	17[a]	64	16	19
n-Hexyl	180°	6	57	0	52	25	28
Cyclohexyl	180–190°	20	54	0	60	15	19
Phenyl	150–160°	5	Trace	0	43	. .	. .
p-Tolyl	170–180°	3	20	0	41	. .	. .

[a] It may be obtained by the thermal rearrangement of ethyl isocyanide initially formed.



$$R{-}N{=}C{=}O + (C_2H_5O)_3P \longrightarrow \left[R{-}N{=}\underset{\underset{\displaystyle O^{\ominus}}{|}}{C}{-}\overset{\oplus}{P}(OC_2H_5)_3\right] \text{ or }$$
$$\text{(V)}$$
$$\underset{\text{(VI)}}{[R{-}N{=}\overset{\oplus}{C}{-}O{-}\overset{\ominus}{P}(OC_2H_5)_3]} \longrightarrow R{-}N{=}C + OP(OC_2H_5)_3$$

R = ethyl, *n*-hexyl, cyclohexyl, and *p*-tolyl

When *n*-hexyl isocyanate was heated with triethyl phosphite at 180–190° for six hours under nitrogen; *n*-hexyl isocyanide was obtained in 57% yield along with a 52% yield of triethylphosphate, and *n*-hexyl isocyanate (25%) and triethyl phosphite (28%) were recovered.

Similarly, ethyl isocyanide and cyclohexyl isocyanide were obtained by the reactions of triethyl phosphite with ethyl isocyanate and cyclohexyl isocyanate, respectively. Besides, *p*-tolyl isocyanide was obtained in a low yield along with a large amount of brownish tarry product, when *p*-tolyl isocyanate was treated with triethyl phosphite at 150–160° for five hours under nitrogen.

An attempt to obtain benzoisonitrile from phenyl isocyanate by a similar reaction was unsuccessful. In this case, a small amount of benzoisonitrile was detectable by its smell, but triethyl phosphate (40%) was the only isolable material by distillation and a large amount of tarry product resulted. The results obtained from the reactions of isocyanates with triethyl phosphite are summarized in Table I.

The results obtained from the reactions of cyclohexyl isocyanate with various trisubstituted phosphites are listed in Table II.

TABLE II

REACTIONS OF CYCLOHEXYL ISOCYANATE WITH TERTIARY PHOSPHITES[a]

	Yield, %		Recovered, %	
$(RO)_3P$ R	C_6H_{11}—NC[c]	$(RO)_3PO$[d]	C_6H_{11}—NCO[e]	$(RO)_3P$
Methyl[b]	0	41	. .	. . .
Ethyl	39	52	35	30[c]
n-Butyl	42	55	40	42[d]
Phenyl	8	5	68	75[d]

[a] Cyclohexyl isocyanate (0.02 mole) and phosphites (0.02 mole) were heated at 190–200° for 7 hr. in a sealed tube. [b] The reaction mixture was black and the isonitrile was not detected by its smell. [c] The yields were determined by method B (see Experimental). [d] They were isolated by fractional distillation and weighed. [e] The yields were determined by method A (see Experimental).

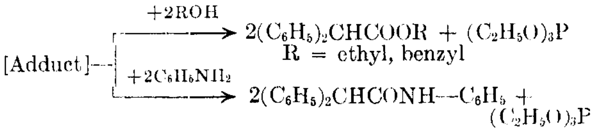
Ethyl isothiocyanate also reacted with triethyl phosphite more readily than ethyl isocyanate, and ethyl isocyanide and triethyl thiophosphate were obtained in 52% and 62% yields, respectively.

$$C_2H_5{-}N{=}C{=}S + (C_2H_5O)_3P \longrightarrow C_2H_5{-}N{=}C + (C_2H_5O)_3PS$$

Next, the reactions of triethyl phosphite with diphenylketene were examined in view of the formal similarity in these two functional groups. Diphenylketene underwent an exothermic reaction with triethyl phosphite at room temperature without solvent or in dry ether to give yellow crystals, m.p. 90–100°. Its structure was confirmed to be a 2:1 addition compound of diphenylketene and triethyl phosphite by analytical data and the result of the recovery of a half amount of triethyl phosphite from the reaction of an equimolar amount of the two. The adduct is unstable in air, but it can be stored for one week in a reduced nitrogen atmosphere.

$$2(C_6H_5)_2C{=}C{=}O + (C_2H_5O)_3P \longrightarrow [\text{Adduct}]$$

When one mole of the adduct reacted with two moles of alcohol or aniline, two moles of the ester of diphenylacetic acid or diphenylacetoanilide were obtained along with one mole of triethyl phosphite.



$$[\text{Adduct}] \xrightarrow{+2ROH} 2(C_6H_5)_2CHCOOR + (C_2H_5O)_3P \quad R = \text{ethyl, benzyl}$$
$$[\text{Adduct}] \xrightarrow{+2C_6H_5NH_2} 2(C_6H_5)_2CHCONH{-}C_6H_5 + (C_2H_5O)_3P$$

On the other hand, when the adduct was pyrolyzed at 215°, diphenylacetylene (40% yield) and triethyl phosphate (69% yield) and white crystals, m.p. 169°, were obtained. The crystals are believed to be the dimer of diphenylketene.[7]

$$[\text{Adduct}] \longrightarrow C_6H_5{-}C{\equiv}C{-}C_6H_5 + (C_2H_5O)_3PO + \text{dimer of diphenylketene}$$

By an improved pyrolysis method, the yield of diphenylacetylene was increased; when 1.5 moles of triethyl phosphite was added at once to one mole of diphenylketene with stirring under nitrogen and heated at 215°, a 65% yield of diphenylacetylene and a 65% yield of triethyl phosphate were obtained along with a small amount of the dimer.

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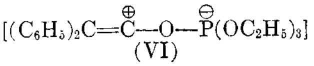
[7] W. Langenbeck and H. Langenbeck, *Ber.*, **61**, 939 (1928).

The yield of diphenylacetylene was calculated on the basis of diphenylketene used.

As shown in the above results, deoxygenation of diphenylketene by triethyl phosphite occurs concomitant with the migration of the phenyl group on the adjacent carbon atom and diphenylacetylene resulted. The intermediate of this reaction is considered to be a similarly coordinated structure (VI), as in the case of isocyanates.


$$[(C_6H_5)_2C{=}\overset{\oplus}{C}{-}O{-}\overset{\ominus}{P}(OC_2H_5)_3]$$

(VI)

Experimental

Material.—Diphenylfuroxane was prepared from phenylnitromethane and phenyl isocyanate according to the method previously reported.[8]

Reaction of Diphenylfuroxane with Triethyl Phosphite.—A mixture of diphenylfuroxane (5.95 g., 0.025 mole) and triethyl phosphite (4.15 g., 0.025 mole) was heated at 160–170° for 5 hr. under nitrogen. The reaction mixture was distilled *in vacuo* giving triethyl phosphate, 4.27 g. (94%), b.p. 86–88° (10 mm.). It showed the same infrared spectrum as that of an authentic sample. Recrystallization of the residue from ethanol gave diphenylfurazan, 5.15 g. (93%), m.p. 93°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.63; H, 4.54; N, 12.61. Found: C, 75.93; H, 4.60; N, 12.41.

Reaction of Azoxybenzene with Triethyl Phosphite.—A mixture of azoxybenzene (6.00 g., 0.030 mole) and triethyl phosphite (6.05 g., 0.036 mole) was heated at 160–170° for 15 hr. under nitrogen. Fractional distillation of the reaction mixture gave triethyl phosphate, 4.36 g. (80%), b.p. 101–103° (20 mm.), and azobenzene, 5.52 g. (91%), b.p. 135–137° (5 mm.), m.p. 68°, mixed m.p. 68°.

Reaction of Ethyl Isocyanate with Triethyl Phosphite.—A mixture of ethyl isocyanate (7.1 g., 0.1 mole) and triethyl phosphite (16.6 g., 0.1 mole) was heated at 180° for 11 hr. in a sealed tube. Fractional distillation of the reaction mixture gave a mixture of ethyl isocyanide and propionitrile, 2.80 g. (51%), b.p. 75–103°, and triethyl phosphite, 3.2 g. (19%), b.p. 52–54° (16 mm.), and triethyl phosphate, 11.6 g. (64%), b.p. 99–101° (16 mm.). The respective yields of ethyl isocyanide (34%) and propionitrile (17%) were determined by gas chromatography. The authentic sample of ethyl isocyanide used for calibration by gas chromatography was prepared according to the described method.[9]

Reaction of *n*-Hexyl Isocyanate with Triethyl Phosphite.—A mixture of *n*-hexyl isocyanate (3.32 g., 0.026 mole)and triethyl phosphite (4.32 g., 0.026 mole) was heated at 180° for 6 hr. under nitrogen and fractionated into two parts. Fraction I weighed 4.25 g., b.p. 40–60° (10 mm.). When *n*-hexylamine (1.0 g.) was added to a solution of 1.00 g. of fraction I in 5 ml. of dry ether, a precipitate of N,N′-di-*n*-hexylurea was obtained. It weighed 0.35 g. The yield of *n*-hexyl isocyanate was 25% calculated from the urea obtained.

Method A.—The filtrate which resulted from above procedure was further analyzed by gas chromatography.

Method B.—It showed that the yields of *n*-hexyl isocyanide and triethyl phosphite were 57% and 28%, respectively. The authentic sample of *n*-hexyl isocyanide used for calibration by gas chromatography was prepared according to the procedure of H. Feuer.[10] Fraction II weighed 2.72 g., b.p. 87–95° (10 mm.). Redistillation of it gave triethyl phosphate, 2.46 g. (52%), b.p. 95–97° (14 mm.).

Reaction of Cyclohexyl Isocyanate with Triethyl Phosphite.—A mixture of cyclohexyl isocyanate (5.00 g., 0.04 mole) and triethyl phosphite (6.65 g., 0.04 mole) was heated at 180–190° for 20 hr. under nitrogen and fractionated into two parts.

Fraction I weighed 4.81 g., b.p. 59–80° (16 mm.): It was worked up in same manner as mentioned above (method A, B). The yields of cyclohexyl isocyanate, cyclohexyl isocyanide and triethyl phosphite were 15%, 54%, and 19%, respectively. The authentic sample of cyclohexyl isocyanide used was prepared by the procedure of Ugi.[11]

Fraction II weighed 5.46 g., b.p. 81–100° (16 mm.). Redistillation of it gave triethyl phosphate, 4.37 g. (60%), b.p. 89–91° (10 mm.).

Reaction of *p*-Tolyl Isocyanate with Triethyl Phosphite.—A mixture of *p*-tolyl isocyanate (3.99 g., 0.03 mole) and triethyl phosphite (4.98 g., 0.03 mole) was heated at 170–180° for 3 hr. under nitrogen. Fractional distillation of the reaction mixture gave *p*-toluisonitrile, 0.72 g. (20%), b.p. 62–63° (6 mm.) and triethyl phosphate, 2.24 g. (41%), b.p. 87–89° (10 mm.). The residue was a brownish tarry product (5 g.). No material was isolated in pure state from the tarry product. The infrared spectra of *p*-toluisonitrile showed a characteristic absorption peak at 4.71 μ.[11]

Reaction of Ethyl Isothiocyanate with Triethyl Phosphite.—A mixture of ethyl isothiocyanate (3.48 g., 0.04 mole) and triethyl phosphite (6.64 g., 0.04 mole) was heated at 150–155° for 3 hr. under nitrogen. The reaction mixture was distilled under reduced pressure and gave ethyl isocyanide, 1.14 g. (52%), b.p. 76–79° and triethyl thiophosphate, 4.86 g. (62%), b.p. 130–132° (35 mm.). Ethyl isocyanide was identified with an authentic sample[9] by gas chromatographic analysis.

Preparation of the Adduct of Diphenylketene and Triethyl Phosphite.—When triethyl phosphite (1.66 g., 0.01 mole) was added to a solution of diphenylketene (1.94 g., 0.01 mole) in 10 ml. of dry ether with stirring at room temperature, the reaction started soon with liberation of heat. The reaction mixture was allowed to stand at room temperature for 5 min. and cooled. The yellow precipitate of the addition compound of diphenylketene and triethyl phosphite was collected and washed with a mixture of ether and petroleum ether and dried *in vacuo*. It weighed 2.70 g. (98%) and melted at 90–100°.

Anal. Calcd. for $C_{34}H_{35}O_5P$: P, 5.6. Found: P, 5.9.

Attempts to recrystallize the adduct from benzene, *n*-hexane, ligroin, and petroleum ether were unsuccessful. Distillation of the filtrate gave triethyl phosphite, 1.23 g. (74%), b.p. 56–57° (21 mm.).

Reactions of the Adduct with Alcohols.—A solution of the adduct (5.55 g., 0.01 mole) in 20 ml. of anhydrous ethanol was warmed on a water bath for 30 min. Ethanol was removed *in vacuo* and a white precipitate was collected. Recrystallization of it from ethanol gave ethyl diphenylacetate, 3.93 g. (82%), m.p. 57–58°, mixed m.p. 58°. Fractional distillation of the filtrate gave triethyl phosphite, 1.19 g. (72%), b.p. 59–60° (23 mm.).

When benzyl alcohol was used in the place of ethanol in the above reaction, benzyl diphenylacetate, 4.78 g. (79%), b.p. 203–205° (1 mm.), m.p. 34°, and triethyl phosphite, 1.02 g. (62%), b.p. 61–62° (24 mm.) were obtained.

Reaction of the Adduct with Aniline.—Aniline (1.90 g., 0.02 mole) was added to a suspension of the adduct (5.55 g., 0.01 mole) in 20 ml. of dry ether and the mixture was refluxed for 1 hr. The yellow color of the adduct soon disappeared and a white solid separated. It was recrystallized from ethanol giving diphenylacetoanilide, 5.38 g. (93%),

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(8) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, **82**, 5339 (1960).

(9) H. L. Jackson add B. C. McKusick, *Org. Syntheses*, **35**, 62 (1955).

(10) H. Feuer, H. Rubinstein, and A. T. Nielsen, *J. Org. Chem.*, **23**, 1107 (1958).

(11) I. Ugi and R. Meyr, *Ber.*, **93**, 239 (1960).

m.p. 178–180°, mixed m.p. 180°. Distillation of the filtrate gave triethyl phosphite, 1.25 g. (75%), b.p. 56–57° (21 mm.).

Pyrolysis of the Adduct.—The adduct (6.99 g., 0.013 mole) was heated at once at 215°. It melted, and a violent reaction occurred and continued for 1 min. The resulting mixture was distilled *in vacuo*. Triethyl phosphate, 0.88 g., 0.005 mole (34%), b.p. 101–102° (18 mm.) and diphenylacetylene, 1.50 g., 0.0084 mole (69%), b.p. 117–121° (3 mm.) were obtained.

Anal. Calcd. for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.10; H, 5.70. Recrystallization of the residue from ethyl acetate gave the dimer of diphenylketene, 2.21 g. (0.0057 mole), m.p. 168–169°.

Anal. Calcd. for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.62; H, 5.17.

When a mixture of the adduct (0.01 mole) and triethyl phosphite (0.02 mole) was pyrolzed under same conditions as mentioned above, triethyl phosphate, 0.012 mole (60%), b.p. 105° (31 mm.) and diphenylacetylene, 0.015 mole (70%), b.p. 120–121° (4 mm.) were obtained and 0.014 mole of triethyl phosphite was recovered.

Pyrolytic Reaction of Diphenylketene with Triethyl Phosphite.—Triethyl phosphite (7.49 g., 0.045 mole) was added to diphenylketene (5.90 g., 0.030 mole) from a separatory funnel with stirring and the mixture was quickly heated at 215–217° under nitrogen. The reaction mixture soon began to boil and a violent reaction continued for 1 min. The resulting mixture was distilled *in vacuo*. Diphenylacetylene, 3.49 g., 0.020 mole (65%), b.p. 125–127° (6 mm.), and triethyl phosphate, 3.56 g., 0.020 mole (65%), b.p. 111–112° (24 mm.), were obtained, and triethyl phosphite, 3.77 g., 0.023 mole, b.p. 61–62° (29 mm.), was recovered. Recrystallization of the residue from ethyl acetate gave the dimer of diphenylketene, 0.13 g., 0.0004 mole (2%), m.p. 167–168°.

Acknowledgment.—The authors wish to express their thanks to Mr. Takanobu Kumamoto for his help during the course of this experiment. Thanks are also due to Mr. Keiji Naruse for the microanalyses.

Microbiological Transformations. XII. The Substrate Specificity of Hydroxylations by a *Penicillium* sp., A.T.C.C. 12,556

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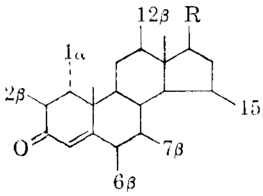
Penicillium sp., A.T.C.C. 12,556, which previously has been reported to hydroxylate C-19 steroids at the 1α-position,[2] failed to introduce a hydroxyl group at this carbon atom in the C-21 steroids, progesterone, 16α,17α-epoxyprogesterone, and 17α,21-dihydroxyprogesterone. Instead, hydroxylation occurred largely at the 7β- and 15β-positions. A 1α-hydroxyl group was introduced into testosterone in low yield by this organism, but hydroxylation also occurred at the 6β-, 12β- and 15β-positions. Testololactone was hydroxylated in the 2β-position. 1α-Hydroxylation with this *Penicillium* sp. appears to be limited to normal C-19 steroids, while 7β-hydroxylation is limited to C-21 steroids.

In a previous paper of this series,[2] the hydroxylation of three C-19 steroids in position 1α and 2β by a *Penicillium* sp. A.T.C.C. 12,556 was reported. Here, we would like to report that 1α-hydroxylation with this organism appears to be limited to normal C-19 steroids. C-21-Steroids were hydroxylated largely at the 7β- and 15β-positions; no 1α-hydroxy C-21 steroid was found. The C-19 steroids, testosterone and testololactone, were both hydroxylated in ring A, but no 7β-hydroxy C-19 steroid was found. We do not believe that this degree of substrate specificity has been reported previously for any organism. Also, by variation of substrate, a total of six different positions were hydroxylated by this versatile mold. To our knowledge this is a record for any one organism.

When progesterone was fermented with this species, the two main products were 15β-hydroxyprogesterone and 7β,15β-dihydroxyprogesterone. These two compounds have been reported earlier by other authors.[3–5]

The configuration of a hydroxyl group at C-15 is sometimes difficult to determine, but the n.m.r. spectrum[6] offers a simple solution to this problem.



The 18-methyl peak is shifted from the value of 9.30 p.p.m. for 15α-hydroxyprogesterone and 9.32 p.p.m. for progesterone to 9.06 p.p.m. for 15β-

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[1] University of Minnesota, Minneapolis 14, Minnesota.

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[3] H. L. Herzog, M. J. Gentles, W. Charney, D. Sutter, E. Townley, M. Yudis, D. Kabasakalian, and E. B. Hershberg, *J. Org. Chem.*, **24**, 691 (1959).

[4] J. Fried, R. W. Thoma, D. Perlman, and J. R. Gerke, U. S. Patent 2,753,290, July 3, 1956. *Chem. Abstr.*, **51**, 2071 (1957).

[5] K. Tsuda, T. Asai, E. Ohki, A. Tanaka, and M. Hattori, *Chem. Pharm. Bull.* (Tokyo), **6**, 387 (1958); K. Tsuda, T. Asai, Y. Sato, T. Tanaka, T. Matsuhisa, and H. Hasegawa, *Chem. Pharm. Bull.* (Tokyo), **8**, 626 (1960).

[6] Kindly determined for us by Dr. N. L. McNiven of the Worcester Foundation for Experimental Biology and the Analytical Department of G. D. Searle, & Co. The curves were run at 60 Mc. in deuterochloroform. The shifts are reported as τ values relative to tetramethylsilane as an internal standard.