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Acid- and Base-catalyzed Rearrangements of a Ring-Chain Tautomeric Ozonide[1,2]

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The stable ring-chain tautomeric ozonide (I ⇆ Ia) from phenylskatole in acetic anhydride was rearranged by acid-catalysis in 90% yield to N-benzoyl-O-acetyl-*o*-aminophenol (III), by pyridine catalysis to the acetylation product of III, *i.e.*, N-benzoyl-N,O-diacetyl-*o*-aminophenol (VI) and to N-acetyl-O-benzoyl-*o*-aminophenol (IV) resulting from III by base-catalyzed acyl migration. This is the first isomerization of a stable ozonide involving a cationoid rearrangement of the type observed previously with peroxides. Infrared data which are given for many mono-, di- and triacyl derivatives of *o*-aminophenol, are an excellent guide in finding the proper location of different acyls at nitrogen and oxygen, respectively. The reduction of diacylamines by lithium aluminum hydride leads to alkylamines and not to dialkylamines.

The reactions carried out with the stable ozonide from phenylskatole[1,3] were interpretable in terms of an equilibrium of this compound between a hydroperoxide "chain" tautomer[4] (Ia, in neutral solution) and the normal isozonide[5] (I) present in basic or acidic solutions as the result of a complex neighboring group effect.[6]

Compounds containing the peroxide element

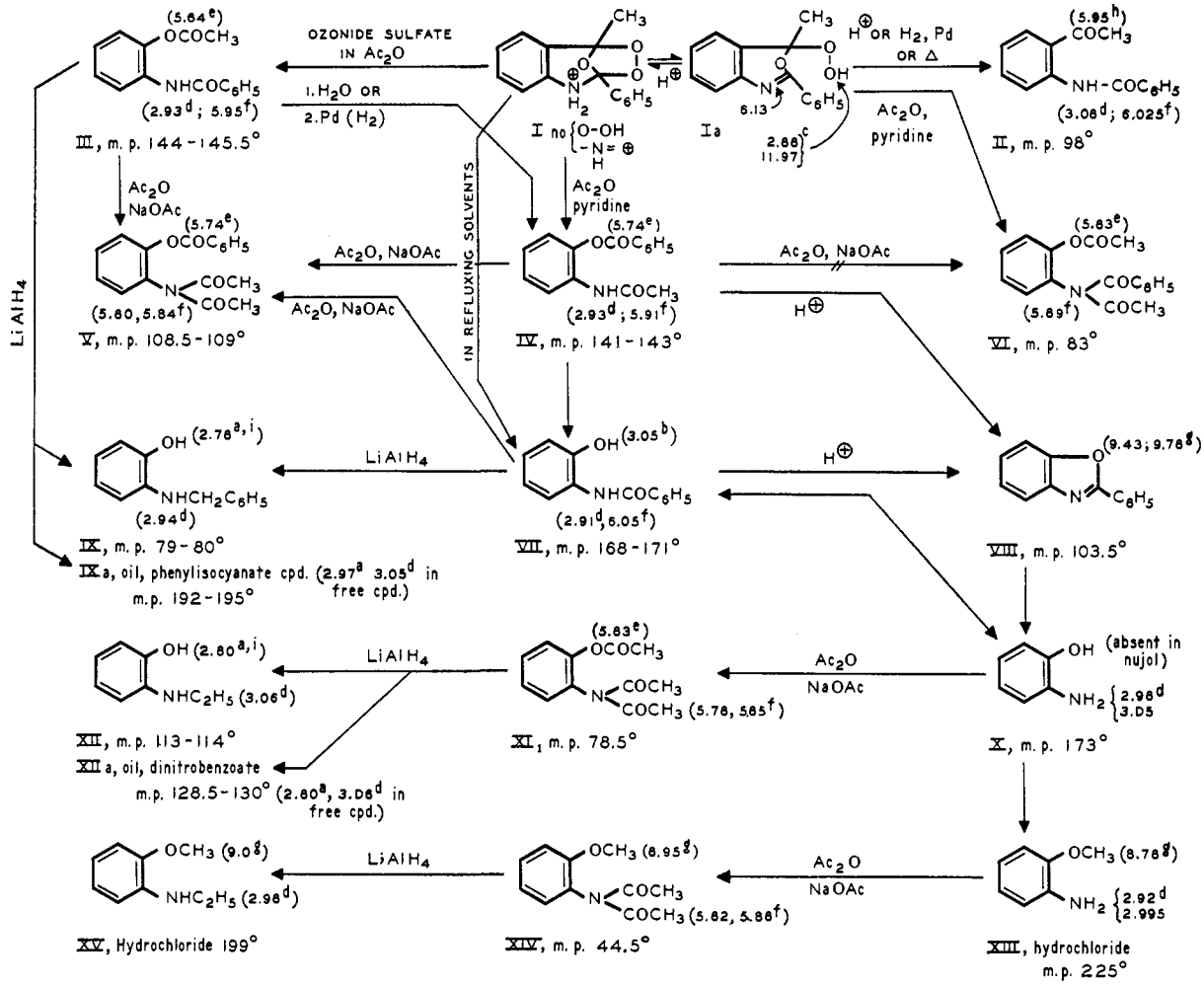


Chart I.—Acid-base catalyzed rearrangements of the ring-chain tautomeric ozonide I ⇄ Ia. The figures in parentheses are infrared absorption bands (all compounds measured in chloroform solution, unless stated otherwise) of the important functional groups with the following assignments: [a] phenolic hydroxyl, non-bonded; [b] phenolic hydroxyl, bonded; [c] hydroperoxy group, possibly bonded, *cf.* hydroperoxides of cumene (2.80), *t*-BuOH (2.84), cyclohexene (2.90), tetralin (2.82): Shreve, Heether, Knight and Swern, *Anal. Chem.*, **23**, 277 (1951); [d] secondary amino group, free and bonded; [e] carbonyl of phenyl benzoate (5.74) or acetate (5.64); [f] carbonyl of amide; [g] C–O–C frequency; [h] carbonyl of conjugated ketone.

–O–O– are known to undergo rearrangements that, as far as they are acid-catalyzed, involve intermediates containing cationoid oxygen.[7] The "acid

(1) On the Mechanism of Oxidation. IV. Preceding paper in this Series, THIS JOURNAL, **74**, 3855 (1952).

(2) Presented in part before the Third Summer Seminar in the Chemistry of Natural Products, July 10-14, 1951, at the University of New Brunswick, Fredericton, New Brunswick.

(3) G. Mentzer, D. Molho and Y. Berguer, *Bull. soc. chim.*, 555 (1950).

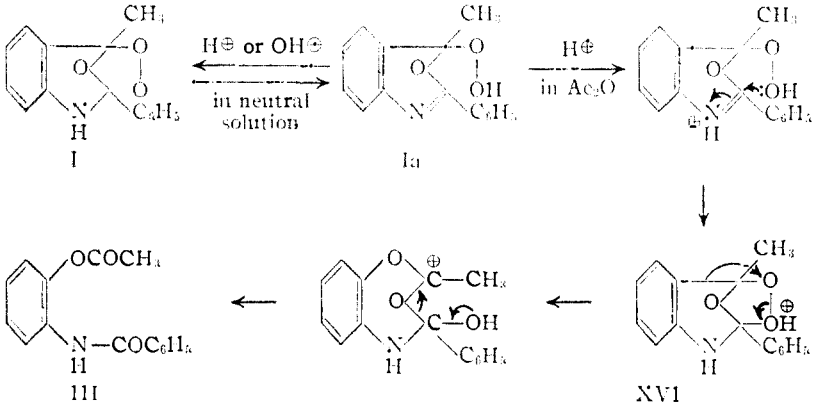
(4) R. Criegee, 120th A.C.S. Meeting, New York, N. Y., September 7, 1951; Abstracts, p. 22M.

(5) H. Staudinger, *Ber.*, **58**, 1088 (1925).

(6) B. Witkop, J. B. Patrick and H. Kissman, H. Wieland Jubilee Volume, *Chem. Ber.*, 85 (1952).

(7) J. E. Leffler, *Chem. Revs.*, **45**, 385 (1949); R. Criegee, *Fortschr. Chem. Forschung*, **1**, 509 (1950).

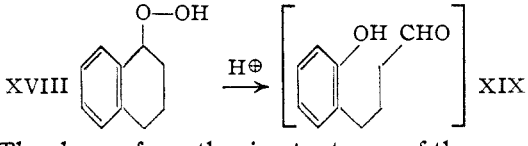
rearrangement" of ozonides,[8] some abnormal ozonizations[7] and the reaction of ozone with carbonyl compounds[7] show that prototropic shifts or migration of suitable groups can occur in ozonides. However,



all these reactions were observed as more or less uncontrolled side reactions in the course of ozonizations. In this paper we describe a sequence of interesting isomerizations of the well-defined salts of the stable ozonide I using a simple and novel experimental technique.

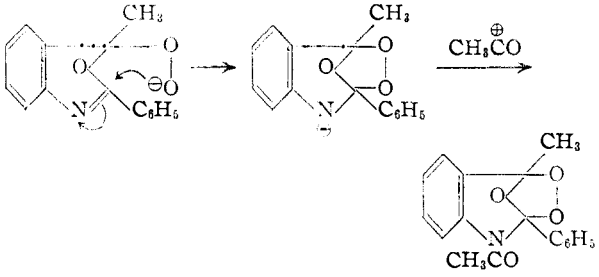
When the crystalline sulfate of the ozonide I was treated under special conditions with excess acetic anhydride,[9] a strongly exothermic reaction occurred. On addition of water there was obtained in over 90% yield a new isomeric crystalline compound, m.p. 144–145.5°, which subsequently was shown to be N-benzoyl-O-acetyl-*o*-aminophenol (III). Since there are in the ring tautomer I four different atoms (the oxirane and the two peroxide oxygens and the imino nitrogen) capable of forming conjugate acids, several mechanisms may be written for this rearrangement, of which we choose one.

The positive charge in XVI is placed at the oxygen of the peroxide bridge to initiate a heterolytic cleavage of the peroxide bond leading to subsequent migration of the phenyl group within the positive ion. This rearrangement is analogous to the migration of aromatic groups in tetralin hydroperoxide (XVIII $\xrightarrow{H\oplus}$ XIX),[10] α-cumyl hydroperoxide[11] [$C_6H_5(CH_3)_2C\text{-}OOH \xrightarrow{H\oplus} C_6H_5OH + CH_3COCH_3$], α-phenylethyl hydroperoxide (giving mainly phenol and no acetophenone, thus showing that phenyl is a better migrator than $H\oplus$ in this reaction)[12] and to the rearrangement of other peroxidic compounds now under investigation.



The change from the ring tautomer of the ozonide (I) to the diacylaminophenol (III) is a *true isomerization*. That acetic anhydride does not participate in this reaction is shown by the use of propionic anhydride which, under the same conditions, leads to the same isomer (III).

Whereas there is only one isomer formed from the ozonide (I) with acetic anhydride using acid-catalysis, a mixture containing at least two products is obtained in the pyridine-catalyzed rearrangement of the ozonide, *viz.*, N-acetyl-O-benzoyl-*o*-aminophenol (IV) and a compound $C_{17}H_{15}NO_4$, m.p. 83°, subsequently shown to be the product resulting from III by acetylation, namely, N-benzoyl-N,O-diacetyl-*o*-aminophenol (VI). The reaction leading to VI probably proceeds through the N-acetyl derivative of the ring tautomer (I) formed by



The isomer IV arises from III by acyl migration catalyzed by the pyridine present in the reaction.

Acyl Migrations.—Such acid–base-catalyzed migrations of acyl residues[13] from nitrogen to oxygen (N → O) or *vice versa* (O → N) occur with all α-amino-β-hydroxy compounds in the aromatic, hydroaromatic[14] and aliphatic[15] series. Acyl derivatives of *o*-aminophenol have been studied in this connection by Stieglitz,[16] Raiford,[17] Bell[18] and LeRosen.[19,20] Hydroxy(benz)oxazolines have been postulated as cyclic intermediates[20] in these reactions in the same way as hydroxy(benz)oxazolidines[21] often represent intermediates in the acyl migrations observed with *cis*-2-aminocyclohexanol,[21] ψ-ephedrine,[15,22,23] and chloroamphenicol (both having been assigned the *cis* or *erythro* conformations on the strength of acyl migration evidence).[24] The ease of rearrangement of mixed

(8) F. G. Fischer, H. Düll and L. Ertel, *Ber.*, **65**, 1468 (1932).

(9) The "chain" tautomer Ia in the absence of acid is so stable that it can be recovered or even recrystallized unchanged from warm acetic anhydride solutions.

(10) M. S. Kharasch, Lecture before the Swiss Chemical Society at Zürich, February 15, 1950, *cf. Angew. Chem.*, **62**, 292 (1950).

(11) Kharasch, Fono and Nudenberg, *J. Org. Chem.*, **15**, 748 (1950).

(12) Kharasch, Fono and Nudenberg, *ibid.*, **16**, 128 (1951).

(13) *Cf.* Theilacker, Migration of Acyl Residues, in Schwab's "Handbuch der Katalyse," **7**, 302 (1943), Springer Verlag, Vienna.

(14) *Cf.* G. Fodor and J. Kiss, *Nature*, **164**, 917 (1949).

(15) L. H. Welsh, THIS JOURNAL, **69**, 128 (1947).

(16) J. Stieglitz, *American Chem. J.*, **21**, 111 (1898).

(17) L. C. Raiford and A. L. LeRosen, THIS JOURNAL, **67**, 2163 (1945), and earlier papers in this series.

(18) F. Bell, *J. Chem. Soc.*, 2962 (1931).

(19) A. LeRosen and E. Smith, THIS JOURNAL, **70**, 2705 (1948).

(20) A. L. LeRosen and E. D. Smith, *ibid.*, **71**, 2815 (1949).

(21) G. Fodor and J. Kiss, *Acta Chimica Acad. Scient. Hungaricae*, **1**, 130 (1951). *Cf.* S. Winstein, L. Goodman and R. Boschan: "Complex Neighboring Groups," THIS JOURNAL, **72**, 4669 (1950); XIIth Int. Congr. Pure Appl. Chem., Abst. Org. Chem., 436, Sept. 1951; E. E. V. Tamelen, THIS JOURNAL, **73**, 5773 (1951); D. F. Elliot, *Chemistry and Industry*, 86 (1952); *Biochem. J.*, **50**, 542 (1952).

(22) V. Bruckner, *et al.*, *J. Org. Chem.*, **14**, 337 (1949).

(23) H. Bretschneider and K. Biemann, *Monatsh.*, **81**, 31 (1950).

(24) G. Fodor, J. Kiss and I. Sallay, *J. Chem. Soc.*, 1858 (1951).

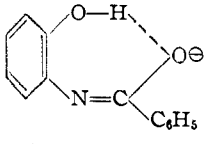
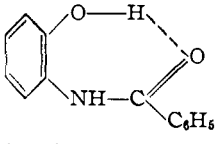
TABLE I: ULTRAVIOLET ABSORPTION DATA OF VARIOUS DI- AND TRIACYL DERIVATIVES OF *o*-AMINOPHENOL

Compound	λ_{max}	log ε	Solvent
N-Benzoyl-O-acetyl-*o*-aminophenol (III)	265	4.085	Chloroform-ether
N-Acetyl-O-benzoyl-*o*-aminophenol (IV)	233	4.415	
	(266)	3.627	Chloroform-dioxane
	266	3.998	
N,N-Diacetyl-O-benzoyl-*o*-aminophenol (V)	243	4.102	Chloroform
N,O-Diacetyl-N-benzoyl-*o*-aminophenol (VI)	246	2.017	Chloroform
N,O,O-Triacetyl-*o*-aminophenol (XI)	263	2.754	Chloroform
N,N-Diacetyl-*o*-anisidine (XIV)	244	3.431	
	281	3.402	Chloroform
N,N-Diacetylaniline	242	3.008	Chloroform
o-Benzaminophenol	(265)	4.125	
	295	2.166	Chloroform

diacyl derivatives of the planar *o*-aminophenol prompted us to look for additional evidence for the proper assignment of acyl groups at the nitrogen and oxygen atoms, respectively. This investigation is summarized in Chart I.

The identification of mixed diacyl derivatives of *o*-aminophenol by means of mixed melting points[18] gives inconclusive results.[19,20] LeRosen and Smith[19,20] used ultraviolet spectrophotometry for the qualitative and quantitative analysis of their pure compounds and equilibration mixtures. We found the ultraviolet spectra (Table I) in this series uncharacteristic and of limited diagnostic value.

We also found the stability of isomer IV (N-acetyl-O-benzoyl-*o*-aminophenol) toward the isomerizing influence of water greater than would be expected from LeRosen's data on the equilibration of mixed diacylaminophenols.[19,20] Infrared spectrophotometry turned out to be an invaluable help in the correct structural assignment of the various acyl groups in the di- and triacyl derivatives listed in Chart I. There is a striking difference between the ester band of a phenyl acetate (5.63 μ) and a phenyl benzoate (5.74 μ).[25] There is also a noticeable difference between N-acetyl (5.80–5.91 μ) and N-benzoyl (5.90–6.05 μ).[26]

XX   XXI

The data presented in the chart suggest distinct ortho-effects which may in turn influence other effects such as hydrogen bonding, association, contribution of betaine structures, etc. Unmistakably there is a bonded hydroxyl (λ 3.05 μ) in N-benzoyl-*o*-aminophenol compared with the non-bonded OH (2.78 μ) in benzylaminophenol, suggestive of some sort of interaction of the carbonyl with the phenolic hydroxyl and leading to the consideration of contributing structures such as XX[27] and XXI.[28] Seven-membered rings containing hydrogen bridges, at one time considered exceptional as in the case of derritol,[29] are now well accepted and used, *e.g.*, for the distinction of the extended and bent forms ("E" and "B" forms) of polypeptide chains.[30]

Peracetylation.—The formation of N-benzoyl-N,O-diacetyl-*o*-aminophenol (VI) directly from the ozonide by acetic anhydride in the presence of pyridine has no precedent. In fact, it proved impossible to obtain this triacyl derivative by any other route. The peracetylation of *o*-benzaminophenol (VII) with acetic anhydride and sodium acetate invariably led to the isomeric N,N-diacetyl-O-benzoyl-*o*-aminophenol (V) also obtained from N-benzoyl-O-acetyl-*o*-aminophenol (III) by the same procedure. These mixed peracyl derivatives in this series have not been described before. We did not observe in our acetylation experiments displacement of the benzoyl group by acetyl as reported previously[17] in the conversion of N-benzoyl-O-acetyl-*o*-aminophenol (III) to N,N-O-triacetyl-*o*-aminophenol (XI).

The positions of the ultraviolet absorption maxima of the peracyl derivatives V and VI do not differ significantly from those of their precursors III and IV (Table I). This shows that any possible contribution of an "imidole"[27] must be small as was found previously for diacylamines.[31] The carbonyl bands in V, VI and XI in the infrared lie at shorter wave lengths (difference 0.06–0.11) than with the diacyl derivatives (III and IV) suggesting some sort of interaction between NH and CO in the latter case.

Lithium Aluminum Hydride Reduction of Di- and Triacylaminophenols.—The reduction of N-benzoyl-O-acetyl-*o*-aminophenol (III) with lithium aluminum hydride furnishes two products: the expected *o*-benzylaminophenol (IX) (m.p. 79°), also obtainable from *o*-benzaminophenol (VII) by the same method, and an oil IXa of which the infrared

(25) The ester bands of simpler model compounds show the following interesting relations (all measurements in chloroform solution):

	Acetate, μ	Benzoate, μ
Phenyl	5.65	5.76
Methyl	5.74	5.78
Benzyl	5.77	5.81

(26) In a similar way as the ester bands the position of the amide bands (in μ) is dependent on the type of substituents and increases in the following order (all measurements in chloroform): N-acetyltetrahydrocarbazole, 5.91; N-benzoyltetrahydrocarbazole, 5.95; N-acetyldiphenylamine, 6.01; acetylmethylamide, 6.00; acetyldimethylamine, 6.10.

(27) This formulation is derived from what A. Hantzsch [*Ber.*, **64**, 661 (1931)] calls the "imidohydrine" or "isoamide" form strongly favored at one time by Hantzsch (ref. above) and Ramart-Lucas [*Compt. rend.*, **196**, 120 (1933); *cf. Bull. soc. chim.*, [5] **4**, 478 (1937)] on the basis of too literally interpreted ultraviolet spectra until F. Arndt and B. Eistert [*Ber.*, **71**, 2040 (1938)] and H. Ley and H. Specker [*ibid.*, **72**, 192 (1939)] pointed out that ultraviolet absorption spectra can fail in the interpretation of certain cases of amide tautomerism. Infrared spectrophotometry again gives a far better picture of the effects of association and enolization contributing to the behavior of amides in solution [*cf.* A. M. Buswell, W. H. Rodebush and M. F. Roy, THIS JOURNAL, **60**, 2444 (1938)].

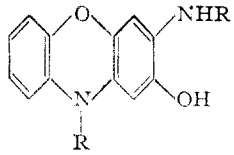
(28) The overlap of intra- and intermolecular hydrogen bonding in these and similar cases is indicated by a large body of spectrophotometric data to be published elsewhere.

(29) S. Takei, S. Miyajima and M. Ōno, *Ber.*, **65**, 104 (1932).

(30) S. Mizushima, T. Shimanouchi, M. Tsuboi and R. Souda, THIS JOURNAL, **74**, 270 (1952); S. J. Leach and H. Lindley, *Nature*, **169**, 360 (1952). Lately even eight-membered rings containing hydrogen bridges have been considered by various authors: W. C. Sears and L. J. Kitchen, *ibid.*, **71**, 4110 (1949); N. D. Coggeshall, *ibid.*, **72**, 2836 (1950); *cf.* R. C. Gore, *Anal. Chem.*, **24**, 9 (1952).

(31) J. B. Polya and T. M. Spotswood, *Rec. trav. chim.*, **68**, 573 (1949); the absence of the imidole form in diacyl amines was further supported by the properties of their metallic derivatives which, unlike those of the diketones, do not form chelated metallic complexes but electrovalent salt-like derivatives that are easily hydrolyzed; L. Hunter and N. G. Reynolds, *J. Chem. Soc.*, 2857 (1950).

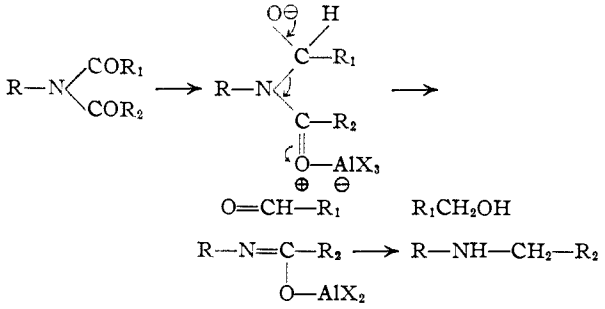
constants (Chart I) and the analytical data of the product with phenyl isocyanate indicate an isomer of so far unknown constitution. This isomer behaves like a phenol and its oily character seems to exclude a bimolecular product such as XXII[32] that could have been formed by autoxidation. A similar oily by-product (dinitrobenzoate, m.p. 128.5–130°) XIIa (infrared constants, Chart I) is obtained in the



XXII

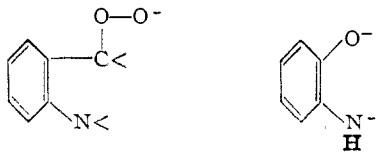
lithium aluminum hydride reduction of N,N,O-triacetyl-*o*-aminophenol (XI) besides the expected *o*-ethylaminophenol (XII). The phenolic hydroxyl, already present or formed by hydrogenolysis from the ester, seems essential for the formation of these oily products, since none of them are observed in the reduction of N,N-diacetylanisidine (XIV). This makes unlikely the possibility of a Stevens rearrangement in the course of the reduction.[33]

The formation of alkylamines rather than dialkylamines from diacylamines with lithium aluminum hydride may be formulated in the following way



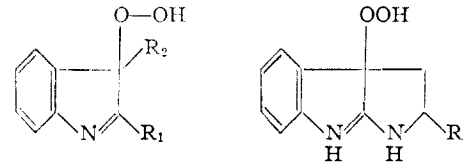
Experiments in progress seem to indicate that in mixed diacylamines hydrogenolysis by lithium aluminum hydride removes acetyl rather than benzoyl. The alcoholysis of diacylamines is somewhat analogous; there the acyl of the stronger acid is removed as ester.[34]

Biochemical Implications.—The possibility of the occurrence of peroxide structures (XXIII) in the normal or abnormal intermediary metabolism of tryptophan has been pointed out already.[35]



XXIII XXIV

Because of its stability and easy accessibility, the ozonide I from phenylskatole was our model compound with which we tested and found the transformation into the *o*-aminophenol series (XXIV). The possibility of such a transformation *in vivo* would be a matter of great interest. Phenylskatole hydroperoxide (XXV), a still more comparable model to the β-hydroperoxyamidine (XXVII) derivable from β-hydroperoxy-ψ-tryptophan (XXVI), has also been rearranged by acetic anhydride and acid catalysis to an isomer, the structure of which is under investigation.



XXV, $R_1 = C_6H_5$; $R_2 = CH_3$ XXVII
XXVI, $R_1 = H$; $R_2 = CH_2—CH(NH_2)COOR$

The hydroperoxide tautomer Ia proved to be too insoluble in aqueous systems to give an indication of possible radiomimetic (mutagenic) properties.[36,37] The preparation and assay of true water-soluble stable ozonides is now in progress.

Experimental[38]

N-Benzoyl-O-acetyl-*o*-aminophenol by Acid-catalyzed Isomerization of the Ozonide (I).—To an ether solution of 200 mg. of 2-phenylskatole ozonide in a centrifuge tube was added concentrated sulfuric acid by drops until no further precipitation was observed. The ozonide sulfate (a light yellow oil) was centrifuged and the cloudy supernatant ether decanted. External cooling was applied to the tube, and 0.5 cc. of acetic anhydride was added dropwise with careful mixing with a stirring rod. The instant reaction led to momentary formation of crystals which subsequently went into a clear, light green solution. The addition of water (10 ml.) caused the immediate formation of a fluffy white crystalline material, which was filtered, washed three times with water, and left overnight over phosphorus pentoxide in a vacuum desiccator. There was obtained a white powder, m.p. 144–145.5°, yield 185 mg. (93%).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.13; N, 5.49; acetyl (mono), 16.86. Found: C, 70.46; H, 5.01; N, 5.61; acetyl, 16.56.

Use of *propionic anhydride* instead of acetic anhydride in the same procedure gave comparable yields of the same product.

N-Acetyl-O-Benzoyl-*o*-Aminophenol (IV). A. By Attempted Hydrogenation of N-Benzoyl-O-acetyl-*o*-aminophenol (III).—A solution of 323 mg. of N-benzoyl-O-acetyl-*o*-aminophenol in 4 ml. of ethyl acetate was stirred under a hydrogen atmosphere in the presence of 50 mg. of prereduced platinum oxide. After 15 minutes the solution was filtered from the catalyst and the clear red filtrate diluted with about four times its volume of pentane at the boiling point, then set aside to crystallize. There were obtained 155 mg. of slightly pink needles, m.p. 130.5–133°. Recrystallization from benzene–pentane raised the m.p. to 134.5° (sublimed in needles 112°; sublimed in droplets 133°; clear colorless melt).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.50; H, 5.42; N, 5.42.

B. By Rearrangement of N-Benzoyl-O-acetyl-*o*-aminophenol with Water.—A suspension of 200 mg. of N-benzoyl-O-acetyl-*o*-aminophenol (III) in 10 ml. of distilled water was refluxed for 30 minutes. On cooling, colorless needles separated. These were filtered off and recrystallized from benzene–pentane. There were obtained colorless needles, m.p. 141–143° (clear colorless melt; subl. in drops from 109°; sublimes in fine needles from 98°).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.65; H, 5.31; N, 5.32.

Although the infrared spectra of the two compounds (IV) obtained by procedures A and B were absolutely identical, their mixed melting points showed a deep depression.

(32) E. Diepolder, *Ber.*, **31**, 495 (1898).

(33) *Cf.* H. Dahn and U. Solms, *Helv. Chim. Acta*, **34**, 907 (1951).

(34) J. B. Polya and T. M. Spotswood, *Rec. trav. chim.*, **67**, 927 (1948).

(35) A. Ek, H. Kissman, J. B. Patrick and B. Witkop, *Experientia*, **8**, 36 (1952).

(36) *Cf.* A. Loveless, *Nature*, **167**, 338 (1951).

(37) We are indebted to Dr. A. Loveless, The Chester Beatty Research Institution, Royal Cancer Hospital, London, for attempting tests in this direction.

(38) All melting points are micro-melting points and corrected; all boiling points are uncorrected.

When the pure compound obtained under the conditions of attempted hydrogenation was refluxed with water for two more hours, recrystallization of the crystals from methanol–water gave crystals, m.p. 136.5°, undepressed on admixture with the starting material.

C. **By Pyridine-catalyzed Rearrangement of 2-Phenylskatole Ozonide** (I).—Two grams of 2-phenylskatole ozonide was covered with acetic anhydride, treated with 3 drops of pyridine, and let stand 24 hours. The mixture was then stirred with 25 cc. of water until the orange oil was replaced by a yellow, pasty, semi-crystalline mass. This was washed twice with cold water, then taken up in ether and dried over potassium carbonate. After filtration, the canary yellow ether solution was evaporated to a volume of approximately 3 cc., diluted with pentane, and set aside to crystallize. The resulting slightly yellow crystals, m.p. 123–139° were recrystallized from benzene, producing long colorless needles, m.p. 132–135° (sublimed in needles 89°; sublimation in drops 101°; clear colorless melt). Admixture of O-benzoyl-N-acetyl-*o*-aminophenol, obtained from the attempted hydrogenation of isomer A, did not depress the melting point (m.p. mixed 133–135°). Depressions were observed on admixture with N-benzoyl-O-acetyl-*o*-aminophenol (117–139°) and O-benzoyl-N-acetyl-*o*-aminophenol obtained by water rearrangement of III (125–134°).

N-Benzoyl-N,O-diacetyl-*o*-aminophenol by Pyridine-catalyzed Rearrangement of the Ozonide (I).—Two grams of 2-phenylskatole ozonide, 6 ml. of acetic anhydride and 2 drops of pyridine were mixed and let stand for 5 days. The mixture was then decomposed with 20 ml. of water, washed thoroughly, and triturated under three more portions of water. The almost colorless powder which resulted was then dried between filter papers, ground in a mortar, and left overnight in a vacuum desiccator over phosphorus pentoxide. The resulting material (1.705 g.) was taken up in approximately 2 ml. of hot benzene, charcoaled, filtered, and set aside to crystallize. After collection and washing there were obtained 340 mg. of colorless needles, m.p. 88–134°. The mother liquor, on dilution with pentane, deposited two types of crystals, needles and plates, but neither melted within a small range. The second mother liquor, on further dilution with pentane, deposited tan plates which were washed twice with benzene and crystallized from benzene–ligroin. The crystals were well-formed colorless polyhedra, m.p. 80–83° (clear colorless melt).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.53; H, 5.04; N, 4.79.

The mother liquor from above was evaporated to dryness and the residue extracted with ligroin and allowed to crystallize from ligroin. Two types of crystals formed: white fluffy needles and large polyhedra. The needles, after recrystallization from ligroin, melted 134–139.5°, and depressed the melting point of N-benzoyl-O-acetyl-*o*-aminophenol (III).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.13. Found: C, 70.20; H, 5.24.

O-Benzoyl-N,N-diacetyl-*o*-aminophenol (V). A. **From N-Benzoyl-O-acetyl-*o*-aminophenol** (III).—A mixture of 40 mg. of N-benzoyl-O-acetyl-*o*-aminophenol (from rearrangement of the ozonide), 40 mg. of fused sodium acetate and 5 ml. of acetic anhydride was refluxed for three hours and then let stand overnight. The acetic anhydride was removed *in vacuo* and final traces removed by leaving the residue in a vacuum desiccator for several hours. Thorough extraction of the residue with ether and evaporation of the ether from the extract left 59 mg. of a brown oil which was extracted repeatedly with hot hexane. Evaporation of the hexane left a yellow oil which deposited crystals on trituration with pentane. Recrystallization of the material from ligroin left slightly yellowish tiny parallelopipeds, m.p. 106.5–108° (slow sublimation from 92°; clear colorless melt).

B. **From *o*-Benzaminophenol** (VII).—A mixture of 275 mg. of *o*-benzaminophenol, 100 mg. of fused sodium acetate and 10 ml. of acetic anhydride was refluxed for four hours. The acetic anhydride was removed *in vacuo* and the residue dried in a vacuum desiccator overnight. Ether extraction of the residue and evaporation of the ether left 378 mg. (98%) of a brown oil. Extraction of the oil with hot hexane yielded a clear yellow oil which, on repeated trituration with cold pentane, deposited colorless crystals, m.p. 102.5–108°. Recrystallization from ligroin afforded colorless parallelopipeds, m.p. 108–109° (slow sublimation from 100°; clear colorless melt). After admixture with material from (A) above, the substance melted at 107–109°.

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.96; H, 5.45; N, 4.80.

C. **From N-Acetyl-O-benzoyl-*o*-aminophenol** (IV).—The acetylation of 15 mg. of N-acetyl-O-benzoyl-*o*-aminophenol (IV, obtained by "hydrogenation" of III) with 10 ml. of acetic anhydride and 100 mg. of sodium acetate (refluxing for two hours) gave a small amount of birefringent colorless prisms after recrystallization from ligroin, m.p. 106.5–108 (sublimation in drops from 104°, clear colorless melt). Mixed melting point with the product obtained under B showed no depression.

***o*-Benzaminophenol** (VII).—Five hundred milligrams of N-benzoyl-O-acetyl-*o*-aminophenol was boiled for five minutes with 15 ml. of 2 *N* hydrochloric acid. A dark curd formed on the surface of the mixture, then set to a crystalline mass. The cooled mixture then was extracted thoroughly with ether and dried over magnesium sulfate. The residue from evaporation of the dry ether solution was taken up in approximately 30 ml. of hot 2 *N* potassium hydroxide, filtered, cooled, and washed thoroughly with ether. The yellow aqueous solution was then boiled to drive off the ether, and, while still hot, was acidified with glacial acetic acid and set aside at 0°. There was obtained 235 mg. of colorless crystals, m.p. 168.5–170° (clear colorless melt; crystalline change to plates around 150°).

Anal. Calcd. for $C_{13}H_{11}NO_{12}$: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.81; H, 5.36; N, 6.64.

2-Phenylbenzoxazole (VIII).[39]—A mixture of 328 mg. of N-acetyl-O-benzoyl-*o*-aminophenol (IV) and 10 ml. of 2 *N* hydrochloric acid was refluxed for 1.5 hours. The reaction mixture was extracted with ether, and the ether extract washed with 2 *N* potassium hydroxide. (The washings, after acidification, extraction with ether, drying, and evaporation afforded some benzoic acid, identified by mixed m.p.). The ether solution was then washed with water, dried over magnesium sulfate, and evaporated. The residue (158 mg.) was recrystallized from 2 ml. of ligroin, yielding 45 mg. of colorless needles, m.p. 101.5–104°.

Anal. Calcd. for $C_{13}H_9ON$: C, 80.00; H, 4.65; N, 7.18. Found: C, 80.31; H, 4.87; N, 7.10.

***o*-Benzylaminophenol** (IX). A. **By Lithium Aluminum Hydride Reduction of N-Benzoyl-O-acetyl-*o*-aminophenol.**—To a suspension of 500 mg. of lithium aluminum hydride in 30 ml. of tetrahydrofuran at 0° was added 1.43 g. of N-benzoyl-O-acetyl-*o*-aminophenol (III). By cautious addition the temperature was maintained at 0°. The yellow reaction mixture was refluxed for one hour, decomposed with ice and filtered. The filtrate was thoroughly extracted with ether and the ether extract was washed with saturated salt solution. After drying over magnesium sulfate, the ether was removed on the steam-bath and the residue sublimed *in vacuo*. A colorless oil of characteristic odor and extreme tendency to autoxidation was obtained at 60° (1 mm.) (see below). The dark residue from the sublimation was charcoaled in boiling methanol, and dried in ether solution over magnesium sulfate. From the brown oil remaining after evaporation of the ether, hot hexane extracted most of the material which crystallized on cooling. Recrystallization from hexane yielded large, thin colorless flakes, m.p. 79–80.5° (clear colorless melt).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.38; H, 6.58; N, 7.03. Found: C, 78.67; H, 6.83; N, 7.45.

B. **By Lithium Aluminum Hydride Reduction of *o*-Benzaminophenol.**—*o*-Benzaminophenol (VII, 317 mg.) was cautiously added to an ice-cold suspension of 300 mg. of lithium aluminum hydride in ether and refluxed for two hours. The mixture was then decomposed with ice, filtered, and the filtrate thoroughly extracted with ether. Evaporation of the ether extracts, following washing with water and saturated salt solution and drying over magnesium sulfate. left 171 mg. of a green oil which was extracted with hot hexane. On cooling, crystals separated from the hexane. The crystals were charcoaled in methanol and recrystallized from hexane: brilliant colorless birefringent flakes, m.p. 79.5–81° (crystalline transformation 68°; clear colorless melt). Mixed melting point with the product obtained under A showed no depression.

(39) *Cf.* M. Bergmann, R. Ulpts and F. Camacho, *Ber.*, **55**, 2806 (1922).

Isomer (?) of *o*-Benzylaminophenol (IXa).—The oil obtained from the vacuum microsublimation had an odor slightly reminiscent of vanillin. On standing in air it rapidly turned green; treated with ferric chloride its methanol solution showed a fleeting blue color followed by a permanent deep red. When the substance in boiling hexane was treated with *phenyl isocyanate* and set aside to cool a crystalline derivative was obtained melting 192–195° (subl. in prisms from 155°; clear colorless melt), after digestion with boiling hexane.

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.43; H, 5.70; N, 8.80. Found: C, 75.30; H, 5.83; N, 8.45.

Treatment of a second portion of the substance with *phenyl isothiocyanate* according to the procedure of Shriner and Fuson yielded a crystalline derivative, m.p. 131–137° after recrystallization from benzene–ligroin.

Anal. Found: C, 64.52; H, 5.41; N, 8.85; residue, 5.82.

Treatment of a third portion of the oil with *α-naphthyl isocyanate* according to Shriner and Fuson yielded a crystalline derivative, m.p. 127–133° after recrystallization from methanol.

Anal. C, 77.90; H, 5.75; N, 5.80.

The amount of material was insufficient for further investigation.

Triacetyl-*o*-aminophenol (XI).[40]—A mixture of 500 mg. of *o*-aminophenol, 100 mg. of freshly fused sodium acetate and 10 cc. of acetic anhydride was refluxed two hours. After removal of the acetic anhydride by distillation *in vacuo*, the residue was freed of traces of solvent by standing overnight, over sulfuric acid in a vacuum desiccator. The residue was then extracted thoroughly with ether and the extract, after filtration, was evaporated to leave a brown oil which, after standing two hours in the vacuum desiccator, amounted to 1.029 g. The oil crystallized readily on trituration with cold pentane. Extraction of the sticky crystalline mass with boiling ligroin produced a clear yellow solution with a strong green fluorescence. On cooling slowly, the solution yielded a first crop of 250 mg. (25%) of magnificent colorless birefringent needles up to 2.5 cm. in length, m.p. 77–78.5° sublimation in drops from 75°; clear colorless melt.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.25; H, 5.57; N, 5.96. Found: C, 61.63; H, 5.72; N, 6.28.

o-Ethylaminophenol (XII).—Three hundred-seventy mg. of N,N,O-triacetyl-*o*-aminophenol was added slowly at 0° to a suspension of 370 mg. of lithium aluminum hydride in 10 ml. of absolute ether. Vigorous evolution of gas was observed. When addition was complete, the mixture was refluxed for three hours, then decomposed with ice and water, mixed with Filter-Aid (Hyflo), and filtered. The organic layer was separated and the brown aqueous layer washed thoroughly with ether. The combined ether layers and washings were then dried over magnesium sulfate (see below). The aqueous phase was brought to *p*H 7 with concentrated hydrochloric acid and 2 *N* potassium hydroxide, then extracted with ether ten times. The yellow ether solution was dried over magnesium sulfate, filtered, and evaporated on the steam-bath, leaving 123 mg. of a red, precrystalline oil which was degassed *in vacuo*. When this residue was taken up in boiling ether, charcoaled, filtered, and allowed to evaporate slowly, crystals were deposited which melted 106.5–111° (sublimation in polyhedra from 65°; softening 84°; green melt) after pentane washing. Sublimation of the substance at 75–95° *in vacuo* on the micro hot stage produced large colorless prisms (birefringent), m.p. 113–114° (subl. in prisms 63°; subl. in drops 105°; green melt). The literature gives 112°[41] for the melting point of *o*-ethylaminophenol.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.03; H, 8.08; N, 10.21. Found: C, 70.27; H, 7.89; N, 10.38.

By-product XIIa.—The first ether extract (see above) was filtered, evaporated on the steam-bath, and degassed *in vacuo* to leave 176 mg. of a red oil of characteristic fragrance. Its infrared spectrum clearly showed that it was not identical with *o*-ethylaminophenol. After being charcoaled in methanol and evaporated, the substance was taken up in ether and allowed to evaporate slowly. Since the substance did not tend to crystallize it was sublimed *in vacuo* on the micro hot-stage up to 70°, and the drop of colorless liquid (highly autoxidizable, turning green on standing) so obtained treated in ether with *3,5-dinitrobenzoyl chloride* and 3 drops of pyridine. The ether was boiled off and the residue heated 5 minutes on the steam-bath, then treated with 4 ml. of water. The red oily precipitate was washed with 2 *N* potassium carbonate, then with water taken up in ether and dried over magnesium sulfate. Evaporation of the dry ether solution left partially crystalline material which was charcoaled in boiling ether, evaporated, and recrystallized from benzene–hexane. A minute amount of crystalline material, m.p. 128.5–130°, was obtained.

N,N-Diacetyl-*o*-anisidine.—A mixture of 0.5 ml. of *o*-anisidine, 100 mg. of freshly fused sodium acetate and 10 ml. of acetic anhydride was refluxed for two hours. After removal of the excess acetic anhydride by distillation *in vacuo*, the residue was thoroughly extracted with ether and the extract, after filtration, evaporated on the steam-bath. The residual brown oil, after two hours in the vacuum desiccator, weighed 916 mg. (theory 840 mg.). The oil resisted crystallization until a small amount of clear light-yellow oil, obtained by hexane extraction, was itself extracted with cold pentane and the pentane solution set aside to evaporate slowly. The resulting beautifully formed clear colorless polyhedra (birefringent) were washed several times with cold pentane and dried under vacuum, m.p. 43–44.5° (clear colorless melt).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 64.28; H, 6.47; N, 6.85.

o-N-Ethylanisidine (XV).—A solution of 675 mg. of N,N-diacetyl-*o*-anisidine (XIV) in 5 ml. of dry ether was added dropwise to 650 mg. of lithium aluminum hydride suspended in ether maintained at 0°. Immediate reaction and vigorous gas evolution was observed. When the addition was complete, the mixture was refluxed for three hours, then decomposed with ice and water, mixed with Hyflo Filter-Aid and filtered. The organic layer in the filtrate was separated and, after the aqueous layer had been washed with ether, the washings were added to it. The resulting ether solution was dried over magnesium sulfate, filtered, evaporated on the steam-bath, and degassed *in vacuo* to leave 373 mg. of an orange oil with a faint odor. The oil was distilled *in vacuo* and the light yellow oil obtained at temperatures up to 75° was dissolved in ether and treated with a solution of hydrogen chloride in ether. The resulting slightly pink oil, after several washings with ether, was allowed to stand overnight, whereupon it formed colorless rodlike crystals which, after recrystallization from methyl acetate–hexane, melted 194.5–199° in a sealed tube on the micro hot-stage. Sublimation, commencing 123°, was too extensive to permit an accurate micro-melting point determination without the sealed tube. Diepolder[42] gives the melting point of N-ethyl-*o*-anisidine hydrochloride as 193°.

N-Ethylaniline.—A solution of 360 mg. of N,N-diacetylaniline in 5 ml. of dry ether was added dropwise at 0° to an ice-cold suspension of 360 mg. of lithium aluminum hydride in ether. When addition was complete the mixture was refluxed for three hours, then decomposed with ice and water, mixed with Hyflo Filter-Aid and filtered under suction. The organic layer was separated and combined with several ether washings from the aqueous layer. The combined ether solutions were dried over magnesium sulfate, filtered, evaporated on the steam-bath, and degassed *in vacuo* to leave 227 mg. of slightly pink oil with a characteristic alkylaniline odor. A portion of this oil was dissolved in ether and treated with an ether solution of hydrogen chloride. The resulting white precipitate was washed three times with fresh ether and dried in a vacuum desiccator; colorless birefringent crystals, m.p. 177–179° (extensive sublimation in drops from 50°; liquid sublimate crystallized in large prisms from 118°, sintering 171°; clear colorless melt). The melting point was not depressed on admixture with authentic ethylaniline hydrochloride.

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(40) *Cf.* E. Diepolder, *Ber.*, **44**, 2500 (1911).

(41) F. H. Lees and F. Shedden, *J. Chem. Soc.*, **83**, 756 (1903).

(42) E. Diepolder, *Ber.*, **31**, 495 (1898).