after recrystallization from heptane followed by sublimation; infrared $\nu_{C=O}^{CCl_4}$ 1688 cm^{-1}; ultraviolet $\lambda_{max}^{isooctane}$ 240 mμ (ε 10,900); the nmr spectrum is presented in the discussion.

Anal. Calcd for $C_{20}H_{23}NO$ (293.39): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.60; H, 8.01; N, 4.89.

Compound 4 Partially Deuterated in the 3 Position.—Deuterium bromide was prepared by action of D_2O on redistilled PBr_3 and the reaction was carried out exactly as for **4**. The nmr spectrum is presented in the discussion.

trans-**1-*t*-Butyl-2-phenyl-3-benzoylazetidine (5). A. From Epimerization of 4.**—A 0.58-g (0.002 mole) sample of **4** and 0.07 g of sodium methoxide in 10 ml of methanol were refluxed for 48 hr. After evaporation of the solvent, the oily residue was extracted with 100 ml of boiling pentane and treated with charcoal. Evaporation of the solvent gave 0.435 g (75%) of **5**: mp 61–63° after recrystallization from heptane and sublimation; infrared $\nu_{C=O}^{CCl_4}$ 1680 cm^{-1}; ultraviolet $\lambda_{max}^{isooctane}$ 242 mμ (ε 15,500); the nmr spectrum is presented in the discussion.

Anal. Calcd for $C_{20}H_{23}NO$ (293.39): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.71; H, 7.88; N, 4.49.

B. From 3 *via* the Bromamino Ketone Hydrobromide.—A 2.93-g (0.01 mole) sample of **3** was dissolved in 100 ml of $CHCl_3$ saturated with HBr and treated exactly as for **4**. The crude extract was analyzed by nmr and showed the presence of 60% **5** and 40% **3**.

C. Compound 5 Deuterated in the 3 Position.—This compound was obtained from **4** as described above using CH_3OD instead of CH_3OH. The nmr spectrum is presented in the discussion.

Anal. Calcd for $C_{20}H_{22}DNO$ (294.39); C, 81.59; H, 7.53; N, 4.75. Found: C, 81.58; H, 7.90; N, 4.50.

Acknowledgment.—This work was supported in part by Grant CA-02931 from the National Cancer Institute of the U. S. Public Health Service.

The Decomposition of Hydrazine Derivatives by Their Reaction with Hydroperoxides

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The reactions of triphenylhydrazine, diphenylpicrylhydrazine, *unsym*-diphenylhydrazine, and tetraphenylhydrazine with hydroperoxides were studied. Diphenylamine was isolated as the main reaction product in all reactions except in the case of tetraphenylhydrazine. The progressive production of free-radical species in the reaction systems was followed by an esr technique and the resulting reaction mixtures were analyzed by gas and column chromatography. A reaction mechanism is proposed.

Although it is known that when amines are warmed with hydroperoxides rapid decomposition of the peroxides occurs to provide the corresponding alcohols, the fate of the amines is not clear. Bickel and Kooyman[1] were unable to isolate any definite compounds derived from the amines. De la Mare[2] investigated the oxidation of secondary amines by hydroperoxides to give carbonyl compounds and the lower amine resulting from carbon–nitrogen bond scission. The hydroperoxides were reduced to the corresponding alcohols. A reaction mechanism was tentatively proposed on the basis of the results obtained by Coppinger and Swalen.[3] On the other hand, Ueda and co-workers[4] have studied the decomposition of diphenylpicrylhydrazyl (DPPH) by hydroperoxide using the esr technique and ascribed the change of the original signal shape to complex formation between DPPH and hydroperoxide. However, this was soon disputed by Möbius and Schneider,[5] who reinvestigated the same reaction spectroscopically in the ultraviolet region as well as using the esr technique. They found that the change of esr signal should be ascribed to the formation of diphenyl nitroxide, but they did not isolate any reaction product. As radicals at concentrations as low as about 10^{-10} mole/l. can be detected by the esr technique, the observation of radical species in the reaction system does not necessarily indicate participation of these radicals in the main reaction route. One must be very cautious about the establishment of reaction mechanisms on the basis of esr study alone.

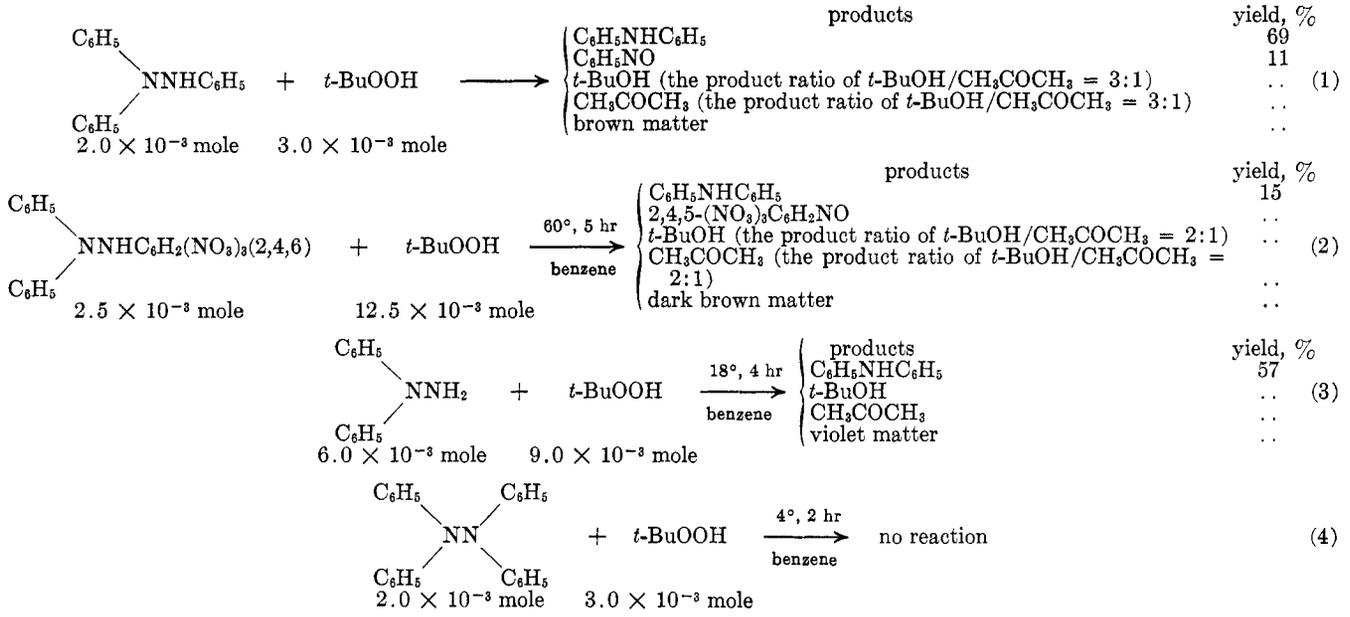
The present authors have studied the reaction of aryl-substituted hydrazine derivatives—triphenylhydrazine, diphenylpicrylhydrazine, *unsym*-diphenylhydrazine and tetraphenylhydrazine—with hydroperoxides—*t*-butyl hydroperoxide and cumyl hydroperoxide—by means of precise analysis of reaction products and by the esr technique in order to clarify unambiguously the mechanism of the reaction of hydrazine derivatives with hydroperoxides.

(1) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 2215 (1956); 2217 (1957).
(2) H. E. De la Mare, *J. Org. Chem.*, **25**, 2114 (1960).
(3) G. N. Coppinger and J. D. Swalen, *J. Am. Chem. Soc.*, **83**, 4900 (1961).
(4) H. Ueda, Z. Kuri, and S. Shida, *J. Chem. Phys.*, **36**, 1676 (1962).
(5) K. Möbius and F. Schneider, *Z. Naturforsch.*, **18a**, 428 (1963).

Results

Triphenylhydrazine, diphenylpicrylhydrazine, and *unsym*-diphenylhydrazine reacted with *t*-butyl hydroperoxide at a fairly rapid rate, but tetraphenylhydrazine did not (eq 1–4). When triphenylhydrazine dissolved in benzene was mixed with *t*-butyl hydroperoxide at *ca.* 4°, the color changed gradually to violet, and finally to dark brown. After 2 hr the reaction mixture was separated by distillation under a nitrogen atmosphere into a volatile fraction and a brown residue. The volatile fraction was analyzed by gas chromatography and the residue was analyzed by column chromatography. Nitrosobenzene, *t*-butyl alcohol, and acetone were identified as components of the volatile fraction. Diphenylamine and nitrosobenzene were found as the major products in the residue. Diphenylpicrylhydrazine reacted with *t*-butyl hydroperoxide more slowly than did triphenylhydrazine, and reaction occurred at an appreciable rate at a higher temperature (60°) to give diphenylamine and trinitronitrosobenzene as the major reaction products.

unsym-Diphenylhydrazine was decomposed by *t*-butyl hydroperoxide at an appreciable rate at room temperature, and only diphenylamine was found as a major product. Tetraphenylhydrazine did not react at temperatures lower than 5°, but it decomposed quite slowly at 50° to give a reaction mixture which had a slightly violet color. After 2 hr almost all of the tetra-



phenylhydrazine (>75%) was recovered from the reaction mixture. All reactions described above were conducted under a nitrogen atmosphere.

A comparison of reaction rates for triphenylhydrazine and for tetraphenylhydrazine was made by titration of the unreacted *t*-butyl hydroperoxide (see Figure 1). The rate of decomposition of *t*-butyl hydroperoxide was much faster in the reaction with triphenylhydrazine than in the reaction with tetraphenylhydrazine. Since *t*-butyl hydroperoxide itself does not decompose below 60° in benzene, the decomposition of the hydroperoxide in the presence of the hydrazine derivatives must have been an induced reaction. When cumyl hydroperoxide was used instead of *t*-butyl hydroperoxide, the above hydrazine derivatives reacted without any essential difference in rate. α,α-Dimethylbenzyl alcohol and a small amount of acetophenone were found in these reactions instead of *t*-butyl alcohol and acetone.

Esr Studies.—These reactions between the hydrazine derivatives and the hydroperoxide were studied by esr spectrometry. Triphenylhydrazine produced three different kinds of radical species as the reaction progressed. Immediately after the reaction components were mixed, a strong esr signal (radical I) was observed. This decayed soon and changed to another signal (radical II) with a hyperfine structure. After 25 min the signal with hyperfine structure attributed to radical II was observed in the reaction system and thereafter the signal began to merge with that of another species (radical III). Finally, after 3 hr, only the spectrum of radical III remained (see Figures 2 and 3). Radical I was assigned to the triphenylhydrazyl structure by comparison with observations made in the oxidation of diphenylpicrylhydrazine as will be explained below. Radical II was relatively stable, and the hyperfine structure corresponding to $C_6H_5\dot{N}OH$ could be analyzed completely (a_N = 11.1 gauss; a_{H_1} = 2.5 gauss, three equivalent hydrogen atoms; a_{H_2} = 0.9 gauss, two equivalent hydrogen atoms). Since a radical which showed an esr signal identical with that of radical II could be obtained by oxidation of phenylhydroxylamine with *t*-butyl hydroperoxide (see Figure 4), radical II was confirmed as being

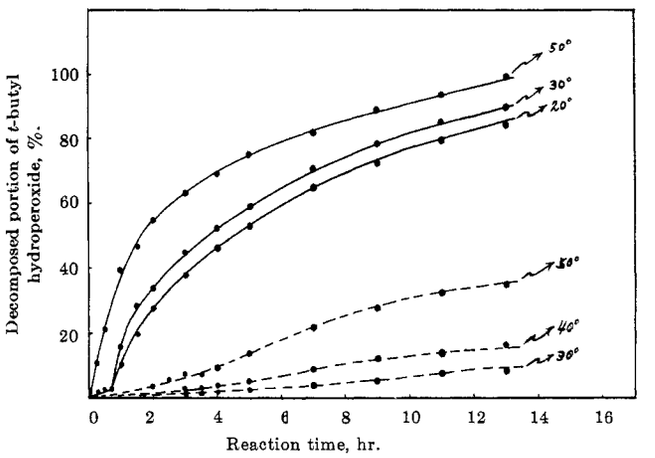


Figure 1.—Decomposition of *t*-BuOOH in reaction system at several temperatures: ————, decomposition of *t*-butyl hydroperoxide in the presence of triphenylhydrazine; - - - - - - - -, decomposition of *t*-butyl hydroperoxide in the presence of tetraphenylhydrazine; reaction conditions, 0.01 mole of *t*-butyl hydroperoxide and 0.01 mole of hydrazine derivative were dissolved in 20 ml of benzene.

$C_6H_5\dot{N}OH$, which was the precursor to nitrosobenzene. Radical III was identified from the analysis of its hyperfine structure as diphenyl nitroxide (a_N = 9.9 gauss, $a_{H_{o,p}}$ = 1.8 gauss, a_{H_m} = 0.9 gauss) which is supposed to be produced by oxidation of diphenylamine and/or its precursor with hydroperoxide.[6]

By oxidation of diphenylpicrylhydrazine with hydroperoxide, a stable radical (radical IV) which was identified as diphenylpicrylhydrazyl from the comparison of its fine structure and total width of esr signal with a DPPH sample was observed at 60° 1 hr after mixing the reaction components (see Figure 5). Then the signal of radical IV gradually started to merge with another signal, and after 3 hr it finally changed to a signal with hyperfine structure which was identical with that of diphenyl nitroxide. In the case of the oxidation of *unsym*-diphenylhydrazine, diphenyl nitroxide was

(6) Y. Deguchi, *Bull. Chem. Soc. Japan*, **35**, 260 (1962); A. L. Buchachenko, *Opt. i Spektroskopiya*, **13**, 795 (1962); J. Thomas, *J. Am. Chem. Soc.*, **82**, 5955 (1960).

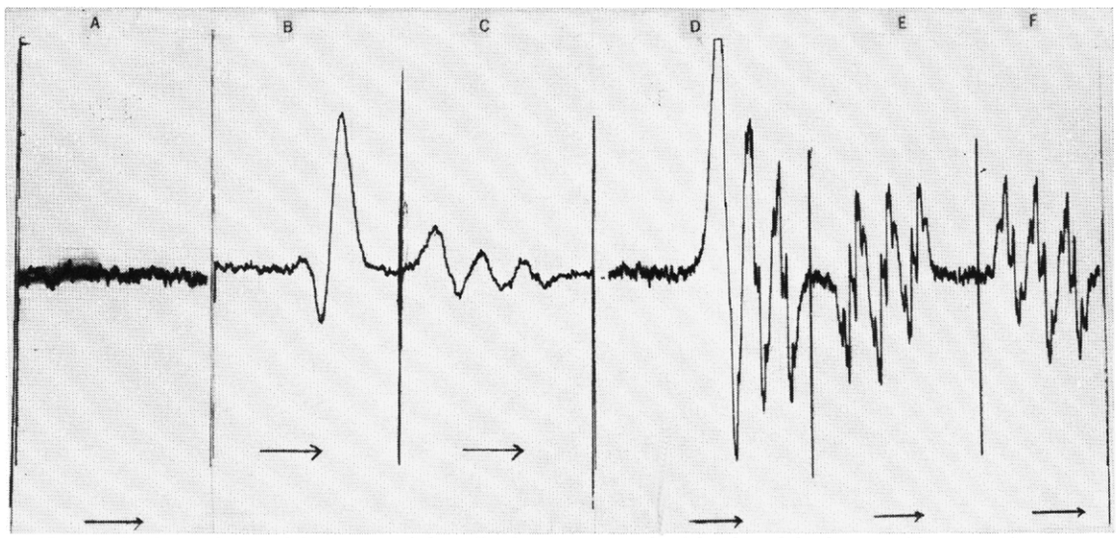


Figure 2.—Free radicals as detected by esr; triphenylhydrazine treated with *t*-butyl hydroperoxide; reaction temperature, 4°; sweep time, 5 min. For A, B, and C: gain, 20; modulation width, 200 mgauss. For D, E, and F: gain, 60; modulation width, 50 mgauss. Figure shows the change of signal shape with time: A, just after mixing of components; reaction does not start yet; B, reaction starts; this signal corresponds to radical I; C, immediately signal changes to that of another radical; D and E, signal intensity becomes gradually weak; F, signal changes to that of stable radical; this radical corresponds to radical II (see Figure 4).

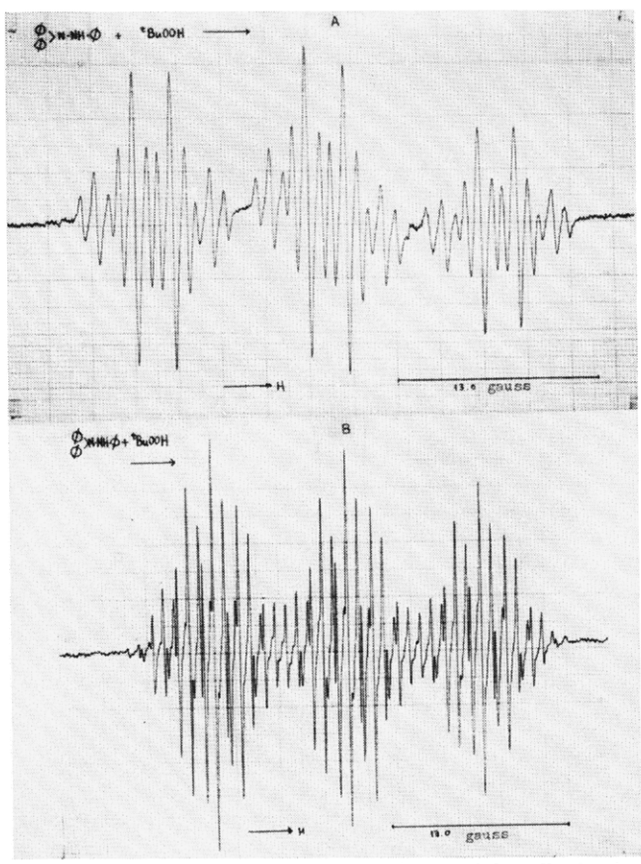


Figure 3.—Free radicals as detected by esr; triphenylhydrazine treated with hydroperoxide; sweep time, 30 min; gain, 60; modulation width, 40 mgauss: A, signal with the more resolved hyperfine structure of F (Figure 2); B, this signal corresponds to that of radical III.

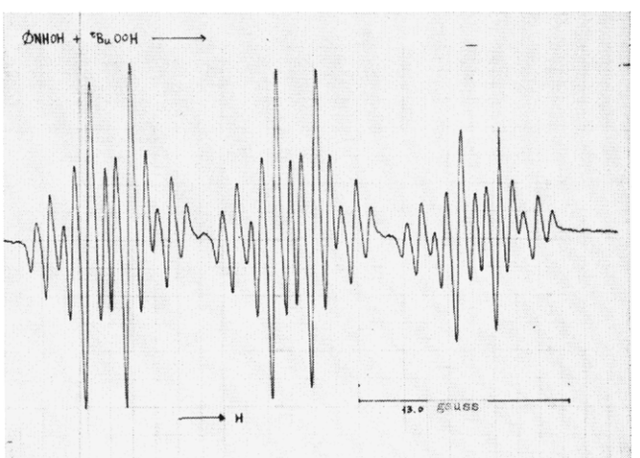


Figure 4.—Esr signal of radical II obtained by oxidation of phenylhydroxylamine with *t*-butyl hydroperoxide.

observed in the reaction system by esr spectrometry (see Figure 6).

Reaction Mechanism.—Although there were differences in product yields, the hydrazine derivatives examined here, with exception of tetraphenylhydrazine, were decomposed to diphenylamine by hydroperoxide. The other half of the molecule changed to a nitrosobenzene derivative or to a nitrogen oxide according to the structure of the original hydrazine. The hydrazines all have a structural feature [as an example, $(C_6H_5)_2NNH$] and this is an essential requirement for a smooth reaction. Since the radical of type $(C_6H_5)_2NNR$ was identified by esr spectroscopy in the reaction system at an earlier stage, it is clear that the decomposition starts with the abstraction of a hydrogen atom from the hydrazine derivative. This is supported by the fact that tetraphenylhydrazine does not react with hydroperoxide at temperatures below 60°. Based on the above discussion, a free-radical mechanism may be proposed for the oxidation of triphenylhydrazine with peroxides, which also may be applied to the other hydrazine derivatives of structure of the type $(C_6H_5)_2NNHR$ (C_6H_5, aryl; R, alkyl or H). This is illustrated in Scheme I. (Asterisked formulas indicate the relatively stable radicals observed by esr.)

The "complex" must be considered because *t*-butyl or cumyl hydroperoxide decompose at about 0° in this reaction system whereas *t*-butyl hydroperoxide itself does not decompose even at 60° in benzene. The very slow decomposition of the hydroperoxide

SCHEME I

Initiation

$$(C_6H_5)_2NNHC_6H_5 + t\text{-BuOOH} \longrightarrow \text{complex}$$

$$\text{complex} \longrightarrow (C_6H_5)_2N{-}\dot{N}C_6H_5 + t\text{-BuO}\cdot + H_2O$$

Propagation

$$(C_6H_5)_2N\dot{N}C_6H_5{}^* + t\text{-BuOOH} \longrightarrow (C_6H_5)_2N\dot{N}C_6H_5 \longrightarrow$$

$$(C_6H_5)_2N\dot{N}C_6H_5(O{-}OBu\text{-}t)(H)$$

$$(C_6H_5)_2N\cdot + NC_6H_5{}^*(OH) + t\text{-BuO}\cdot$$

$$(C_6H_5)_2N\cdot + (C_6H_5)_2NNHC_6H_5 \longrightarrow$$

$$(C_6H_5)_2N\dot{N}C_6H_5{}^* + (C_6H_5)_2NH$$

Termination

$$C_6H_5\dot{N}OH + t\text{-BuO}\cdot \longrightarrow C_6H_5NO + t\text{-BuOH}$$

$$t\text{-BuO}\cdot \longrightarrow CH_3COCH_3 + \cdot CH_3$$

Side reaction

$$(C_6H_5)_2NH \text{ or } (C_6H_5)_2N\cdot + t\text{-BuOOH} \longrightarrow (C_6H_5)_2NO + t\text{-BuOH}$$

which is observed in the reaction system containing tetraphenylhydrazine and *t*-butyl hydroperoxide at 50° must be an induced decomposition by $(C_6H_5)_2N\cdot$ radicals. They could exist in the reaction mixture since tetraphenylhydrazine can dissociate into $(C_6H_5)_2N\cdot$ radical although in very low concentration.[7]

Experimental Section

Starting Materials.—Tetraphenylhydrazine was synthesized by oxidation of diphenylamine with potassium permanganate,[8] mp 145°. Triphenylhydrazine was synthesized through the reaction of phenylhydroxylamine and phenylmagnesium bromide following the method discovered by Busch and Hobein,[9] mp 141–142°. Diphenylpicrylhydrazine was prepared by the reaction between *unsym*-diphenylhydrazine and picrylchloride,[10] mp 173.5–174°. *unsym*-Diphenylhydrazine was used after the purification of the commercial special grade hydrochloric acid salt. *t*-Butyl hydroperoxide and cumyl hydroperoxide were synthesized by usual methods. *t*-Butyl hydroperoxide had bp 38–39° (23 mm); cumyl hydroperoxide had bp 65° (0.18 mm).

Reaction between Hydrazine Derivatives and Hydroperoxide.—Triphenylhydrazine (0.002 mole) was dissolved in 50 ml of benzene and the solution was cooled to about 4°; after that *t*-butyl hydroperoxide (0.003 mole) was added all at once to the solution. After several seconds, the reaction mixture started to become violet, then suddenly changed to dark brown. The reaction mixture was distilled under nitrogen atmosphere and was separated into a volatile fraction and a residue. By gas–liquid partition chromatography (stationary phase, Apiezon grease L, 30%; support, Celite 545, 80–100 mesh, 200 cm long), it was confirmed that the volatile fraction contained *t*-butyl alcohol, acetone, and nitrosobenzene. The latter was determined spectroscopically using the absorption band at 284 mμ. The residue was separated by column chromatography on silicic acid using petroleum ether (bp 30–50°) as the elution solvent. Di-

(7) H. Wieland, *Ann.*, **381**, 200 (1911).

(8) L. Gatterman, "Die Praxis des Organischen Chemikers," Walter de Grunter, Berlin, 1954, p 308.

(9) M. Busch and R. Hobein, *Ber.*, **40**, 2100 (1907).

(10) S. Goldschmidt and K. Renn, *ibid.*, **55**, 636 (1922).

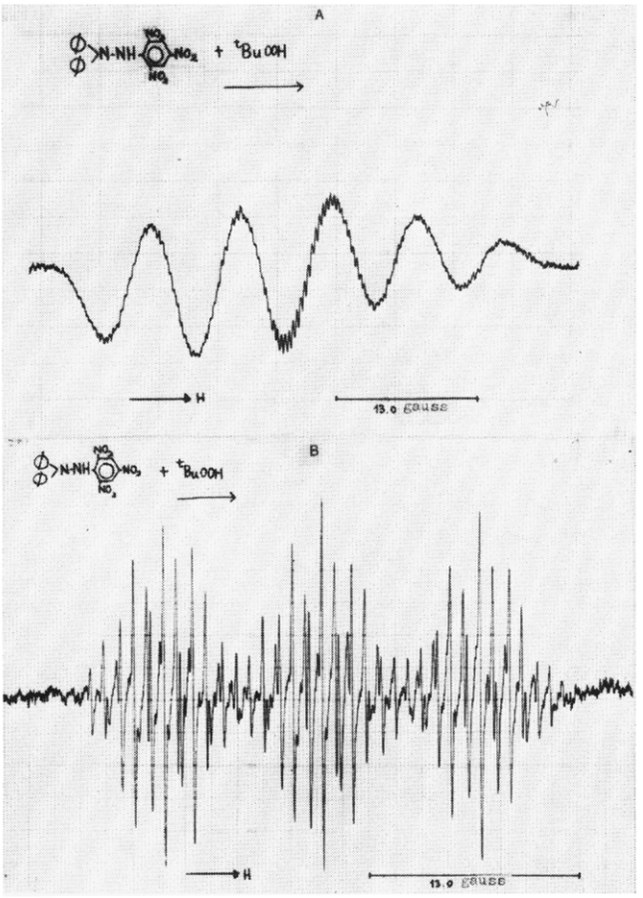


Figure 5.—Free radicals as detected by esr; diphenylpicrylhydrazine treated with hydroperoxide: A, signal of radical IV; this is identical with that of DPPH; B, signal A changes gradually to this signal corresponding to that of diphenyl nitroxide radical.

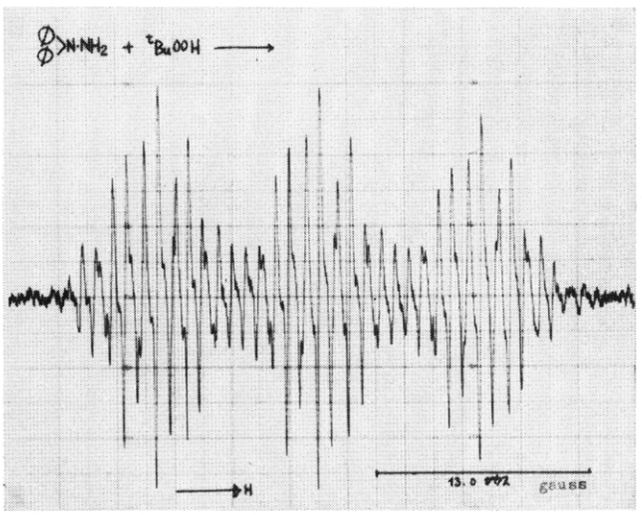


Figure 6.—Free radical as detected by esr; *unsym*-diphenylhydrazine treated with hydroperoxide; this radical observed is identical with diphenyl nitroxide.

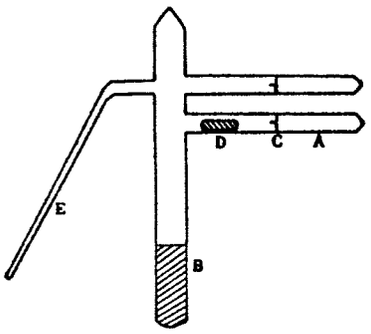


Figure 7.—Reaction vessel: A, *t*-butyl hydroperoxide; B, solution of hydrazine derivative; C, breakable seal; E, this part was inserted into the cavity.

phenylamine (white plates, mp 54°), nitrosobenzene, and a small amount of unidentified colored matter were isolated from the residue. For the other hydrazine derivatives, the reaction procedure and analyses of the reaction products were essentially identical with the above. Trinitronitrosobenzene which was obtained from the reaction mixture of diphenylpicrylhydrazine with hydroperoxide was crystallized as brown plates, mp 194–195°. This was identified by elemental analysis (*Anal.* Calcd for N: 23.14. Found: 24.15.), by nmr (τ 5.55), by thin layer chromatography, by its absorption maxima at 239, 322, and 406 mμ, and by mixture melting point determination with the authentic sample.[11]

Studies by Esr Spectrometer.—Esr measurements on the reaction mixture containing hydrazine derivative and hydroperoxide were done as follows using a 3BX-Type spectrometer with 100-kc modulation manufactured by Japan Electron Optics Lab. A known amount of the previously completely degased hydroperoxide was sealed in a small vessel with a break seal on one side. This side was fused to the other vessel in which a known amount of the completely degased benzene solution of the hydrazine derivative was sealed (see Figure 7). The break seal was destroyed at the desired temperature with a hammer, the reaction components were mixed, and the progression of the reaction was followed in the cavity of the esr spectrometer.

Titration of Hydroperoxide.—The remaining hydroperoxide was extracted from the reaction mixture by a known amount of water at 15°. The hydroperoxide extract was analyzed by the usual iodometry. The value obtained was corrected by a factor of 100/42.3.

(11) R. Nietzki and R. Ditschy, *ibid.*, **34**, 59 (1901).

Some Unusual Reactions of Hydrazines with a Hindered Steroidal α-Amino Ketone[1]

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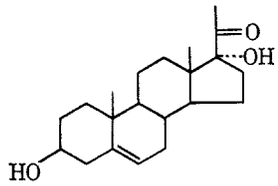
Received July 18, 1966

The reaction of 17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (**2c**) with hydrazine or methylhydrazine afforded, after mild acid hydrolysis, the reduced product, 17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (**2f**). Similar treatment of **2c** with 1,1-dimethylhydrazine yielded the oxidized product, 17a-methyl-D-homoandrosta-5,17-diene-3β,17-diol-16-one (**6a**). The hindered dimethylamino group of **2c** underwent a novel "pseudo-allylic" 1,3-displacement by primary and secondary amines (including hydrazines), affording the corresponding 16β-amino-17aβ-methyl-D-homo 17-ketones (**7**, **12**, **13**). The further reactions of the 16-hydrazino-17-keto intermediates (**7**) to the final products is discussed.

We have previously reported the rearrangement of 17α-hydroxy-20-keto steroids (**1**) to D-homo-17aα-amino 17-ketones (**2a**, **b**) when heated at 200° with ammonia or methylamine.[2] The structure of this series of compounds was well established by both chemical and physical methods.[2] During the course of our structure elucidation work, however, a series of anomalous reactions was encountered. This paper describes these reactions and the observations that resulted from them.



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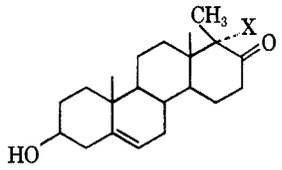

2a, X = NH_2
b, X = NHMe
c, X = NMe_2
d, X = $NMeCH_2C_6H_5$
e, X = OH
f, X = H
g, X = OAc of **f**

The nitrogen atom in compounds of series **2** is severely sterically crowded, as indicated by resistance of the secondary amine **2b** to acetylation, of the tertiary amine **2c** to quaternization with methyl iodide, and of the corresponding amino alcohols (from **2a** and **b**) to cleavage by periodate at 65°.[2] This loss in reactivity of the amine group in these compounds caused by the steric hindrance about C-17a led us to consider the Kishner reductive-elimination reaction as a means of structure elucidation.

The reaction of hydrazine or its derivatives with ketones having a variety of α substitutents (*e.g.*, hydroxyl, epoxy, halo, cyclopropyl, etc.) affords olefins in many instances.[3] Leonard has shown that even an α-amino ketone can be reduced to an olefin by this reaction if the amino group is sufficiently hindered.[4] It was already shown that the corresponding D-homo-α-hydroxy ketone (**2e**) readily underwent Kishner reductive elimination to the D-homo 17-olefin (**3a**).[3c,5] On the basis of Leonard's work, it

(1) Presented at the Gordon Research Conference on Steroids and Other Natural Products, New Hampton, N. H., Aug 5, 1966.

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(3) (a) N. Kishner, *J. Russ. Phys. Chem. Soc.*, **45**, 973 (1913); (b) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704 (1952); (c) R. B. Turner, R. Anliker, R. Helbling, J. Meier, and H. Heusser, *Helv. Chim. Acta*, **38**, 411 (1955); (d) D. H. R. Barton, N. J. Holness, and W. Klyne, *J. Chem. Soc.*, 2456 (1949); (e) D. E. Ames and R. E. Bowman, *ibid.*, 2752 (1951); (f) E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963); (g) W. R. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964); (h) P. S. Wharton, S. Dunny, and L. S. Krebs, *ibid.*, **29**, 958 (1964); (i) C. L. Bumgardner and J. P. Freeman, *Tetrahedron Letters*, 737 (1964); (j) S. M. Kupchan and E. Abushanab, *ibid.*, 3075 (1965); (k) Huang-Minlon and Chung-Tungshun, *ibid.*, 666 (1961); (l) C. Djerassi, D. H. Williams, and B. Berkoz, *J. Org. Chem.*, **27**, 2205 (1962); (m) C. Djerassi and G. von Mutzenbecker, *Proc. Chem. Soc.*, 377 (1963); (n) B. T. Gillis and J. D. Hagarty, *J. Am. Chem. Soc.*, **87**, 4576 (1965).

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(5) (a) H. Heusser, N. Wahba, and F. Winternitz, *Helv. Chim. Acta*, **37**, 1052 (1954); (b) L. Ruzicka and H. F. Meldahl, *ibid.*, **23**, 513 (1940).