

A NEW STABLE FREE RADICAL (1)

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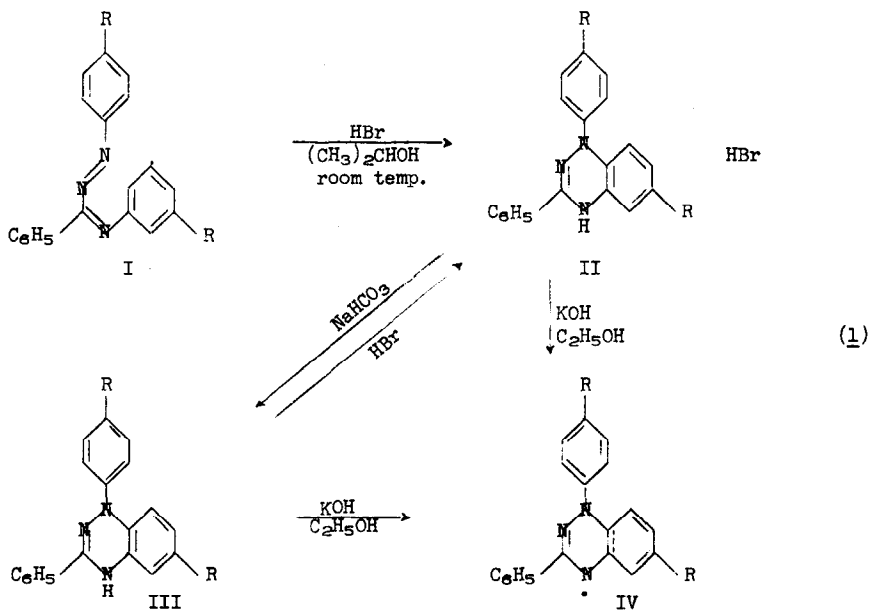
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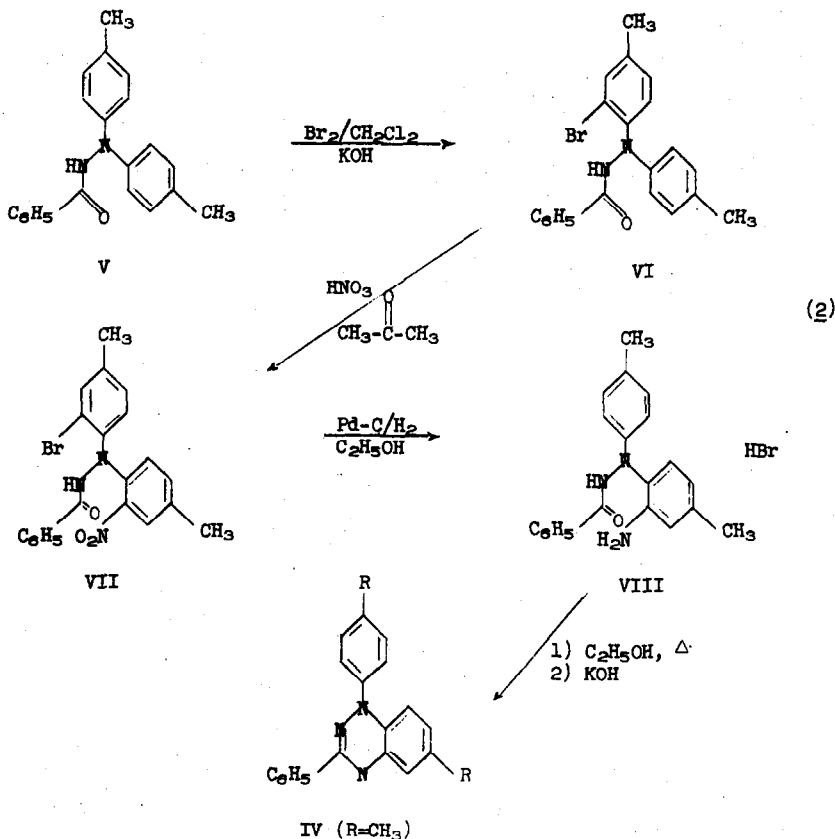
To the growing list of stable organic free radicals (2) there can now be added the 1,2,4-benzotriazinyl free radicals as exemplified by the parent 1,3-diphenyl-1,2,4-benzotriazinyl radical (IV, R=H) depicted in eq. (1). The stability of this new type of heterocyclic free radical (3) appears to be comparable at least to that of the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) (4,5), which has frequently been used as a calibration standard for electron paramagnetic resonance investigations (e.p.r.).

These substances may be best prepared by the synthetic scheme illustrated in eq. (1). The addition of 7 ml of HBr/2-propanol solution (6) to 1.0 g of N'-phenyl-N-phenyliminobenzami-



dine (I, R=H) (7) at room temperature rapidly (2-3 min) yielded the yellow 2-propanol insoluble salt, (1,4)-dihydro-1,3-diphenyl-1,2,4-benzotriazine hydrobromide (II, R=H) { 0.9 g (70%) after one recrystallization from methanol-diethyl ether; anal. sample m.p. $\sim 235^\circ\text{d}$ [$\text{CH}_3\text{OH}-(\text{C}_2\text{H}_5)_2\text{O}$]; λ_{max} (CH_3OH) 250 μ (ϵ 23,200), 300 shoulder (6,750), 344 sh (4,120), 430 sh (950), λ_{min} 224 (ϵ 15,150); Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{BrN}_3$: C, 62.31; H, 4.41; N, 11.47. Found: C, 62.53; H, 4.48; N, 11.44 }. Careful treatment of II (R=H) with aqueous sodium bicarbonate liberated the yellow diethyl ether soluble free base III (R=H) [m.p. $105-7^\circ\text{d}$ (8) (diethyl ether-pentane); λ_{max} (CH_3OH) 216 μ sh (ϵ 20,274), 248 (21,976), 302 (8,171), 336 sh (5,577), 420 sh (1,073), λ_{min} 226 (16,544), 283 (7,288); infrared (Nujol): 3307 cm^{-1} (NH, m), Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_3$: C, 79.97; H, 5.30; N, 14.73. Found: C, 79.71; H, 5.26; N, 14.77]. Re-conversion of III (R=H) to the hydrobromide salt II (R=H) could be readily achieved in diethyl ether solution with HBr/2-propanol thereby eliminating the possibility of further deep-seated changes. Although the 1,3-diphenyl-1,2,4-benzotriazinyl free radical (IV, R=H) may be generated by a number of methods, including air oxidation, the cleanest appeared to be the treatment of II (R=H) or III (R=H) at room temperature over a period of several hours with ethanolic aqueous potassium hydroxide (9). For example, 0.75 g of the free base III (R=H) was converted quantitatively by this method to the free radical IV (R=H) which crystallized out as beautiful black needles, m.p. $113-15^\circ$ ($\text{C}_2\text{H}_5\text{OH}$) [Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_3$: C, 80.26; H, 4.96; N, 14.78. Found: C, 80.56; H, 4.95; N, 14.78; infrared (Nujol and CH_2Cl_2): no -NH stretching frequency; λ_{max} (CH_3OH) 260 μ sh (ϵ 33,020), 268 (36,130), 320 (7,150), 370 (5,490), 420 sh (2,630), 490 (1,330), 570 sh (540); λ_{min} 230 (11,230), 300 (4,480), 340 (3,300), 473 (1,110)]. The total absence of an observable p.m.r. spectrum (10) together with the broadening of the tetramethylsilane reference signal is in complete accord with the paramagnetic nature (2b,11,12) of the 1,3-diphenyl-1,2,4-benzotriazinyl free radical (IV, R=H). That this substance and certain related derivatives such as IV (R= CH_3) exist entirely in the free radical form in the solid state and also in solution is clear from e.p.r. spectral comparisons (3) with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. Their stability is so marked that they themselves could conceivably be utilized as standards.

To reinforce our thesis concerning the unusual ring closure of I to II depicted in eq. (1) it was incumbent upon us to develop an alternative and unambiguous route to these 1,2,4-benzotriazine compounds. This was accomplished as outlined in eq. (2). Benzoic 2,2-bis-(p-



tolyl)-hydrazide (V), m.p. 198-200° (CH₃OH) [λ_{\max} (CH₃OH) 220-26 μ plateau (ϵ 19,360), 280 (13,920), λ_{\min} 254 μ (7,670); Anal. Calcd for C₂₁H₂₀N₂O: C, 79.71; H, 6.37; N, 8.85. Found: C, 79.57; H, 6.38; N, 8.59], prepared by benzoylation of the known N,N-di-p-tolyl-hydrazine hydrochloride (V) (13), could be monobrominated in fair yield in methylene chloride in the presence of a saturated aqueous potassium hydroxide solution to benzoic 2-(2-bromo-p-tolyl)-2-(p-tolyl)-hydrazide (VI) (14), m.p. 212-14° (CH₃OH) [λ_{\max} (CH₃OH) 224 μ sh (ϵ 24,570), 279.5 (11,580), λ_{\min} 256 μ (ϵ 7,270); Anal. Calcd for C₂₀H₁₈BrN₂O: C, 63.80; H, 4.85; N, 7.08. Found: C, 63.35; H, 4.93; N, 7.24.]. After numerous unsuccessful attempts the vital mononitration of VI was finally achieved in cold acetone solution using an equimolar amount of concentrated nitric acid added dropwise. A poor to fair yield of the pure yellow crystalline benzoic 2-(2-bromo-p-tolyl)-2-(2-nitro-p-tolyl)-hydrazide (VII) was obtained, m.p. 218-220° (diethyl ether) [λ_{\max} (CH₃OH) 220 μ sh (ϵ 29,240), 266 (16,800), 390 (1,890), λ_{\min} 249 (14,580), 345 (1,430); Anal. Calcd for C₂₁H₁₈BrN₃O₃: C, 57.28; H, 4.12; N, 9.54.

Found: C, 56.99; H, 4.29; N, 9.66.]. The crucial conversion of VII to VIII, which involved both hydrogenation of the nitro group and hydrogenolysis of the bromo substituent, was readily accomplished at atmospheric pressure in ethanol over 10% Pd-C. The slightly hygroscopic off-white salt VIII (15) was isolated in good yield (78%), m.p. 210-12°d (CH₃OH-diethyl ether) [λ_{\max} (CH₃OH) 234 μ (ϵ 27,840), 264 sh (6,230), 272 sh (4,700), λ_{\min} 218 (23,490); Anal. Calcd for C₂₁H₂₂BrN₃O: C, 61.17; H, 5.38; N, 10.19. Found: C, 60.77; H, 5.89; N, 10.04.]. Upon refluxing an ethanolic solution of 0.5 g of VIII for five hours (16) with subsequent concentration to a minimal volume and addition of ethanolic potassium hydroxide there was obtained 0.22 g (59%), after one recrystallization from ethanol, of 6-methyl-3-phenyl-1-(p-tolyl)-1,2,4-benzotriazinyl free radical (IV, R=CH₃) as beautiful black crystals, m.p. 123-5° (C₂H₅OH) [Anal. Calcd for C₂₁H₁₈N₃: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.81; H, 5.92; N, 13.74; infrared (Nujol and CH₂Cl₂): no -NH stretching frequency; λ_{\max} (CH₃OH) 268 μ (ϵ 36,270), 329 (7,810), 374 (7,340), 495 (1,550), 570 sh (700), λ_{\min} 230 μ (ϵ 14,770), 301 (4,210), 347 (4,700), 475 (1,400)]. Once again, the total absence of an observable p.m.r. spectrum (10) together with the broadening of the tetramethylsilane reference signal is in accord with the observations previously noted for the 1,3-diphenyl-1,2,4-benzotriazinyl free radical (IV, R=H). E.P.R. spectral comparisons (3) show that IV (R=CH₃) also exists as a 100% free radical in the solid state and in solution. To eliminate any vestige of residual doubt, 6-methyl-3-phenyl-1-(p-tolyl)-1,2,4-benzotriazinyl free radical (IV, R=CH₃) was also prepared by the original route depicted in eq. (1) (17). The black crystals so obtained were identical in all respects with those isolated by the alternative route [eq. (2)]. The circuit was then completed.

We plan to elaborate on these results in a forthcoming publication. Clearly, the potential areas worthy of further investigation are quite broad.

REFERENCES

1. Presented in part by H. M. Blatter at the First International Congress of Heterocyclic Chemistry, The University of New Mexico, Albuquerque, New Mexico, June, 1967; paper No. 111 of the Abstracts.
2. Some leading references are: a) G. W. Wheland, "Resonance in Organic Chemistry", John Wiley and Sons, Inc., New York, N.Y., 1955, p. 391. b) E. M. Kosover and E. J. Foziomex, *J. Am. Chem. Soc.*, **86**, 5515 (1964). c) R. Kuhn, F. A. Neugebauer, and H. Trischmann, *Monatsh. Chem.*, **98**, 726 (1967).
3. The 1,3-diphenyl-1,2,4-benzotriazinyl free radical (IV, R=H) seems to be stable indefinitely. The beautiful black crystals have been kept in ordinary glass vials for slightly more than

two years without any apparent physical or spectral changes. The e.p.r. spectral measurements on a 10 month old sample indicated that this substance existed entirely as a 100 percent free radical both in the crystalline state and in benzene solution. Comparisons were made with a standard, the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical (see footnotes 4 and 5). We are indebted to Dr. H. Loeliger, CIBA Limited, Basle, Switzerland, for the e.p.r. results herein reported.

4. A. L. Buchachenko, "Stable Radicals", Consultants Bureau, New York, N.Y., 1965.
5. D. E. Williams, *J. Am. Chem. Soc.*, 88, 5665 (1966).
6. The ring closure rate did not appear to be unduly dependent upon the acid concentration of the solution. Our typical solutions were prepared by passing gaseous hydrogen bromide rapidly through a liter of reagent grade 2-propanol for 10-15 minutes with external cooling.
7. M. Busch and R. Ruppenthal, *Chem. Ber.*, 43, 3001 (1910). The facile reductive reconversion of I (R=H) in our hands to benzanilide 2-phenylhydrazone ($C_6H_5NHN=C-NH-C_6H_5$) at atmospheric pressure in ethanol over 10% Pd-C is in complete accord with the structural assignment.

$$\begin{array}{c} | \\ C_6H_5 \end{array}$$
8. a) A mixture melting point with I (R=H), m.p. 101-2°, was considerably depressed. b) All melting points given in this communication are uncorrected.
9. The actual base concentration does not appear to be a crucial factor at least in a synthetic sense. A typical reaction solution might consist of 2 g of II (R=H), 25 ml of ethanol, 15 ml of water, and 5-6 pellets of 87.2% assay potassium hydroxide (approximately 0.7-0.9 g).
10. In deuteriochloroform solution with tetramethylsilane as the internal reference at 60 Mcps.
11. J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, N.Y., 1959, p. 207.
12. R. Breslow and Hai Won Chang, *J. Am. Chem. Soc.*, 87, 2200 (1965).
13. R. H. Poirier and F. Benington, *J. Org. Chem.*, 19, 1157 (1954).
14. Although the possibility of para bromination was excluded by the deliberate inclusion of methyl groups blocking the para positions, we have not rigorously eliminated the possibility that VI is actually the meta substituted bromo isomer. Since hydrogenolysis occurs as desired later in the scheme, the position of the bromo atom is not germane to the overall concept. The introduction of a bromo atom was linked to our inability to mononitrate V directly.
15. This structure has been somewhat arbitrarily assigned since we have not attempted to assess the possibilities of ring-chain tautomerism and N to N benzoyl migration. The ring closure [VIII \rightarrow IV (R=CH₃)] would proceed in any event via the ring tautomer regardless of the exact nature of VIII.
16. Ultraviolet monitoring indicated a build-up of II (R=CH₃) [see eq. (1)]. Its spectrum was essentially identical, of course, to that of II (R=H).
17. Full details will be presented in a forthcoming publication. The properties of all compounds encountered in the synthesis of VI (R=CH₃) by the initial route [eq. (1)] were in agreement with their structures. Of the two ortho positions available for ring closure [I \rightarrow II (R=CH₃)] it was apparent that the less hindered position was highly favored.