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Benzodiazepines. IX.[1] Oxidation of N-Phthalimidoacetylindoles

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Chromic acid oxidation of N-phthalimidoacetylindoles (**4**) caused cleavage of the indole 2,3-double bond affording the expected 2′-benzoyl-2-phthalimidoacetanilides (**5**). Ozonolysis, on the other hand, resulted in the formation and isolation of the stable crystalline ozonides (**6**). Ozonides (**6**) as well as **5** were shown to be converted into benzodiazepin-2-one (**7**) by treatment with hydrazine hydrate.

In previous publications[3] of this series, the oxidative ring enlargements of 2-aminomethylindoles and 1-aminoethylindoles to the respective 1,4-benzodiazepin-2-ones and 1,4-benzodiazepines have been reported. We wish to report now on the oxidation of N-phthalimidoacetylindoles.

N-Phthalimidoacetylindole (**4a**) was prepared by acylation of hydrazone (**1**) with phthalimidoacetyl chloride followed by the Fischer cyclization of the resulting N^1-phthalimidoacetylhydrazone (**3**) with polyphosphoric acid or zinc chloride, while **4b** was prepared by acylation of N-unsubstituted indole (**2b**) with phthalimidoacetyl chloride and sodium hydride in dimethylformamide. An attempt to remove the protective phthaloyl group of **4a** with hydrazine hydrate and obtain N-glycylindole led to cleavage of the N–CO bond and the formation of **2a**.

For oxidation of **4** chromic acid and ozone were used as oxidants. Chromic acid oxidation of **4a** led only to the formation of 2′-benzoyl-4′-chloro-2-phthalimidoacetanilide (**5a**). The reaction probably proceeds *via* the dicarbonyl intermediate (**5c**), from which the formyl group would be removed by oxidation or hydrolysis to give **5a**. In contrast to **4a**, **4b** gave, under similar conditions, a mixture of the dicarbonyl derivative (**5b**) (55%) and **5a** (21%). The structure of **5b** was supported by the elemental analysis and by the infrared (IR), nuclear magnetic resonance (NMR) and mass spectra.

In several cases stable ozonides have been isolated, although only from ozonolysis of 2,3-disubstituted indoles.[4] Most of the stable ozonides have been derived from 2-aryl-3-alkylindoles, and shown to be capable of a ring–chain tautomerism between **8a** and **8b** by Witkop and co-workers.[5] In contrast Ockenden and Schofield[6] have found that only when the mobility of the system is restricted by N-acetylation,[7] ozonides of 2,3-dimethyl- and

1) Part VIII: K. Ishizumi, S. Inaba and H. Yamamoto, *J. Org. Chem.*, **37**, 4111 (1972).
2) Location: *2-1, Takatsukasa-4-chome, Takarazuka-shi, Hyogo.*
3) *a*) H. Yamamoto, S. Inaba, T. Hirohashi and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); *b*) S. Inaba, T. Hirohashi and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1263 (1969); *c*) S. Inaba, K. Ishizumi and H. Yamamoto, *ibid.*, **19**, 263 (1971); *d*) S. Inaba, K. Ishizumi, K. Mori and H. Yamamoto, *ibid.*, **19**, 722 (1971); *e*) S. Inaba, K. Ishizumi, T. Okamoto and H. Yamamoto, *ibid.*, **20**, 1628 (1972).
4) *a*) P.S. Bailey, *Chem. Rev.*, **58**, 925 (1958); *b*) R.J. Sundberg, "Organic Chemistry: The chemistry of Indoles," Academic Press, Inc., New York and London, 1970, Chapter V.
5) *a*) B. Witkop, J.B. Patrick and H.M. Kissmann, *Chem. Ber.*, **85**, 949 (1952); *b*) B. Witkop and J.B. Patrick, *J. Am. Chem. Soc.*, **74**, 3855 (1952).
6) D.W. Ockenden and K. Schofield, *J. Chem. Soc.*, **1953**, 612.
7) In the case of 2,3,6-trimethylindole, a small yield of a crystalline ozonide is obtained in ethyl acetate at −20°.[6]

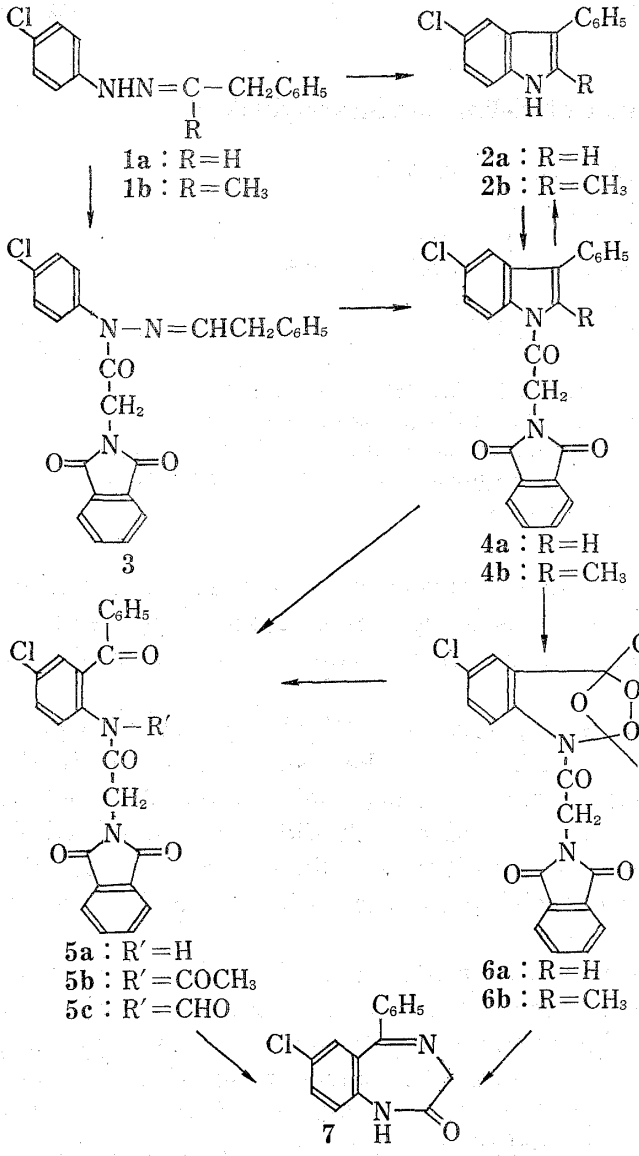
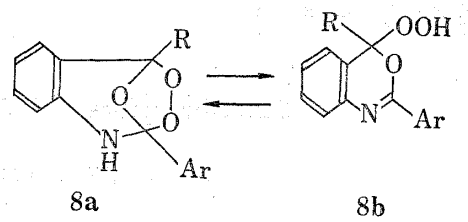


Chart 1



8a 8b

Chart 2

2,3,5-trimethylindole, and tetrahydrocarbazole can be isolated in ethyl acetate although in poor yields.

When compounds (**4**) were ozonized with an excess of ozone–oxygen stream in acetic acid, stable ozonides (**6**) were obtained in high yields, despite the general tendency[6] of the use of acetic acid as the solvent to give only 2-acylaminoarylketones. The structural assignment for ozonides (**6**) were based on the elemental analyses and the IR spectra which showed the carbonyl absorptions ascribable to a phthalimidoacetyl group, but not the benzophenone bands in 1620—1670 cm^{-1} region.

Since the ozonolysis of 2-methyl-3-phenylindole in acetic acid is known[6] to yield only 2′-benzoylacetanilide, it is considered, in agreement with Schofield's observations, that substitution of the acyl group in position 1 increases the stability of ozonides. The isolation of **6a** indicates, furthermore, that a substituent in position 2 is not always necessary to obtain a stable crystalline ozonide.

Ozonide (**6a**), when heated in ethanol, afforded a quantitative yield of **5a**, whereas **6b** gave a complex mixture of products. Compound (**5a**) is considered to be formed by the loss of carbon dioxide from **6a**.

Compound (**5a**) was converted to benzodiazepin-2-one (**7**) by hydrazinolysis as described in the literature.[8] The same treatment of **5b** also gave **7** with no observable formation of 1-acetylderivative of **7**. It is interesting to note that ozonides (**6**) were directly converted to **7** by hydrazinolysis.

Experimental

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were measured on a Hitachi Model EPI-G3 spectrophotometer, and NMR spectra on a Varian A-60D instrument using tetramethylsilane as an internal standard. Mass spectrum was taken on a Shimadzu LKB instrument

8) Delmar Chem. Ltd., Netherlands Patent 6500446 [*C. A.*, **64**, 5120 (1966)].

with the direct sample inlet system; ionizing potential at 70 eV. The drying agent used for organic solutions was anhydrous sodium sulfate.

Phenylacetaldehyde N¹-Phthalimidoacetyl-(*p*-chlorophenyl)hydrazone (3)——To a solution of 28.8 g of *p*-chlorophenylhydrazine in a mixture of 150 ml of ethanol and 30 ml of acetic acid was added 27.5 g of phenylacetaldehyde at 10—15° over a period of 15 min. The mixture was stirred at room temperature for 1 hr and at 72—78° for 15 min. The solvent was evaporated and the residue was partitioned between aqueous ammonia and ether. The organic layer was separated, washed with water, dried, and concentrated. Crystallization of the residue from hexane gave 42.7 g (86.2%) of phenylacetaldehyde *p*-chlorophenylhydrazone (**1**), mp 66—79°.

A mixture of 20 g of phthalimidoacetic acid and 35 g of thionyl chloride was refluxed for 1 hr. The excess thionyl chloride was evaporated and the residue was dissolved in 80 ml of tetrahydrofuran (THF). The solution of phthalimidoacetyl chloride obtained was added to a mixture of 20 g of **1**, 7.7 g of pyridine and 160 ml of THF at −1——5° over a period of 40 min. The reaction mixture was stirred at −1° for 5 hr and allowed to stand at the same temperature overnight. Insoluble material was separated by filtration and the filtrate was evaporated to dryness. Recrystallization of the residue from ethanol afforded 19.2 g of **3**, mp 158—163°. A second crop (3.1 g, mp 156—161°) was obtained from the mother liquor to give a combined yield of 22.3 g (63.4%). Further recrystallization from ethanol gave yellow plates, mp 169.5—171.5°. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1715, 1705, 1620, 1600. *Anal.* Calcd. for $C_{24}H_{18}O_3N_3Cl$: C, 66.75; H, 4.20; N, 9.73; Cl, 8.21. Found: C, 67.09; H, 4.32; N, 9.67; Cl, 8.27.

5-Chloro-3-phenyl-1-phthalimidoacetylindole (4a)——A mixture of 15 g of **3** and 75 g of polyphosphoric acid was heated to 180° for 20 min and then poured into ice-water. The precipitate was collected by filtration, washed with water and recrystallized from ethanol to give 2.3 g of **4a**, mp 232—234°. A second crop (1.5 g) was obtained from the mother liquor to give a combined yield of 3.8 g (26.4%). IR ν_{max}^{Nujol} cm^{-1}: 1775, 1710. NMR (DMSO-d_6) δ: 5.40 (2H, s, CH_2), 7.3—8.5 (13H, m, aromatic protons and C_2–H). *Anal.* Calcd. for $C_{24}H_{15}O_3N_2Cl$: C, 69.49; H, 3.64; N, 6.75; Cl, 8.55. Found: C, 69.29; H, 3.54; N, 6.69; Cl, 8.46.

Compound (**4a**) (mp 232—234°) was also obtained by heating **3** to 215° with zinc chloride in 21% yield.

5-Chloro-2-methyl-3-phenylindole (2b)——A mixture of 25 g of *p*-chlorophenylhydrazine and 50 g of phenylacetone was stirred and heated at 80° for 2 hr. The mixture was partitioned between water and ether. The ether layer was dried and evaporated. Distillation of the residue at 170—175° (0.5—0.6 mmHg) gave 21 g (62.2%) of **2b**, mp 78—83°. Recrystallization from aqueous isopropanol afforded plates, mp 89—91.5°. IR ν_{max}^{Nujol} cm^{-1}: 3430 (NH). *Anal.* Calcd. for $C_{15}H_{12}NCl$: C, 74.53; H, 5.00; N, 5.79; Cl, 14.67. Found: C, 74.64; H, 4.95; N, 5.77; Cl, 14.82.

5-Chloro-2-methyl-3-phenyl-1-phthalimidoacetylindole (4b)——To a solution of 15 g of 5-chloro-2-methyl-3-phenylindole in 450 ml of dimethylformamide was added 3.24 g of 69% sodium hydride dispersion in liquid paraffin at −10°. The mixture was stirred at −5° for 2 hr, and then phthalimidoacetyl chloride, prepared from 19.1 g of phthalimidoacetic acid and thionyl chloride, was added at −5—3°. The resulting mixture was stirred for 2 hr at −1° and allowed to stand overnight in a refrigerator. The precipitate formed was collected by filtration, washed with ether and dried to give 3.0 g of **4b**, mp 250—253°. The filtrate was poured into 1000 ml of water. The precipitate was collected by filtration and recrystallized from acetone to give an additional 4.0 g of **4b**, mp 254—255° for a combined yield of 7.0 g (26.3%). Recrystallization from dimethylformamide afforded slightly yellow needles, mp 254—255°. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1720, 1695. *Anal.* Calcd. for $C_{25}H_{17}O_3N_2Cl$: C, 70.02; H, 4.00; N, 6.53; Cl, 8.27. Found: C, 70.14; H, 4.07; N, 6.64; Cl, 8.03.

Treatment of 4a with Hydrazine Hydrate——To a solution of 0.20 g of **4a** in a mixture of 10 ml of chloroform and 10 ml of ethanol was added a mixture of 0.05 g of hydrazine hydrate and 0.05 ml of water. The mixture was stirred overnight at room temperature, and the gelatinous precipitate of phthalhydrazide formed was separated by filtration. After evaporation of the filtrate, the residue was recrystallized from ligroin to give 0.05 g (45.5%) of **2a**, mp 91—91.5° (lit.[9] mp 91°). IR ν_{max}^{Nujol} cm^{-1}: 3430. *Anal.* Calcd. for $C_{14}H_{10}NCl$: C, 73.85; H, 4.43; N, 6.15; Cl, 15.57. Found: C, 74.01; H, 4.23; N, 6.11; Cl, 15.43.

2′-Benzoyl-4′-chloro-2-phthalimidoacetanilide (5a)——To a suspension of 1.0 g of **4a** in 10 ml of acetic acid was added a solution of 1.0 g of chromic anhydride in 1 ml of water at 13—15°. The mixture was stirred at room temperature for 18 hr. The precipitate formed was collected by filtration, washed with water and dried to give 0.70 g (69.4%) of **5a**, mp 207—209°. Recrystallization from methanol afforded colorless prisms, mp 211—212° (lit.[8] mp 207—208°). IR ν_{max}^{Nujol} cm^{-1}: 3240, 3200, 1770, 1710, 1635. NMR ($CDCl_3$) δ: 4.56 (2H, s, CH_2), 7.25—8.70 (12H, m, aromatic protons), 11.08 (1H, s, NH). *Anal.* Calcd. for $C_{23}H_{15}O_4N_2Cl$: C, 65.96; H, 3.61; N, 6.69; Cl, 8.46. Found: C, 65.71; H, 3.39; N, 6.44; Cl, 8.39.

N-Acetyl-2′-benzoyl-4′-chloro-2-phthalimidoacetanilide (5b)——To a suspension of 1.0 g of **4b** in 10 ml of acetic acid was added a solution of 0.63 g of chromic anhydride in 0.6 ml of water at 12—17°. The mixture was stirred at room temperature for 22.5 hr. Unchanged **4b** (0.13 g) was recovered by filtration. The filtrate was poured into 100 ml of water, and the precipitate was collected by filtration, washed with water

9) P. Bravo, Gaudiano and A. Umani-Ronchi, *Tetrahedron Letters*, **1969**, 679.

and dried. Crystallization of the solid (0.85 g) from ethanol gave a mixture of colorless needles and pillars, the former being **5a** and the latter **5b**. The mixture was suspended in hexane and separated by decantation to yield 0.176 g (20.7% based on unrecovered **4b**) of **5a**, mp 199—207° and 0.252 g of **5b**, mp 171—179°. The original ethanol filtrate gave an additional 0.264 g of **5b**, mp 177—181° for a combined yield of 0.516 g (55.2% based on unrecovered **4b**). An analytical sample was obtained after recrystallization from ethanol as colorless pillars, mp 181—184°. IR ν_{max}^{Nujol} cm^{-1}: 1784, 1736, 1729, 1707, 1670. NMR (C_5D_5N) δ: 2.25 (3H, s, CH_3), 5.12 (2H, s, CH_2), 7.20—7.95 (12H, m, aromatic protons). Mass Spectrum *m/e*: 460 (M^+), 418, 400, 273, 255, 230. *Anal.* Calcd. for $C_{25}H_{17}O_5N_2Cl$: C, 65.15; H, 3.72; N, 6.08; Cl, 7.69. Found: C, 65.43; H, 3.85; N, 6.08; Cl, 7.71.

TLC analysis of the filtrate indicated the presence of a small amount of 2′-benzoyl-4′-chloroacetanilide.

5-Chloro-3-phenyl-1-phthalimidoacetylindole Ozonide (6a)——Into a suspension of 1.0 g of **4a** in 20 ml of acetic acid was passed a stream of ozone-oxygen at 19—21°. The precipitate formed was collected by filtration and dried to give 0.60 g of **6a**, mp 164—165° (decomp.). The filtrate was diluted with water and the resulting precipitate was collected by filtration to give an additional 0.30 g of **6a**. The total yield was 0.90 g (80.7%). The ozonide oxidized sodium iodide solution to liberate iodine. IR ν_{max}^{Nujol} cm^{-1}: 1772, 1710. *Anal.* Calcd. for $C_{23}H_{15}O_4N_2Cl$: C, 62.27; H, 3.27; N, 6.05; Cl, 7.66. Found: C, 62.18; H 2.87; N, 6.32; Cl, 7.86.

The ozonide **6a**, dissolved in hot ethanol, gave a quantitative yield of **5a**.

5-Chloro-2-methyl-3-phenyl-1-phthalimidoacetylindole Ozonide (6b)——A suspension of 1.0 g of **4b** in 20 ml of acetic acid was ozonized as described above. The insoluble material was filtered off and the filtrate was diluted with water. The resulting precipitate was collected by filtration to give 0.95 g (85.5%) of **6b**, mp 98—109° (decomp.). The ozonide gave a positive active oxygen test. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1715. *Anal.* Calcd. for $C_{25}H_{17}O_6N_2Cl$: C, 62.97; H, 3.59; N, 5.87; Cl, 7.43. Found: C, 62.64; H, 3.75; N, 5.59; Cl, 7.42.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7)——A. From **5a**: To a suspension of 0.3 g of **5a** in a mixture of 3.3 ml of ethanol and 3.3 ml of chloroform was added a mixture of 0.07 g of hydrazine hydrate and 0.07 ml of water. The mixture was stirred at room temperature for 1.5 hr, and the resulting solution was allowed to stand overnight. The gelatinous precipitate of phthalhydrazide formed. The solvent was evaporated and the residue was partitioned between ether and 0.7% aqueous ammonia. The ether layer was then extracted with 5% hydrochloric acid. The acidic layer was made basic with 10% aqueous sodium hydroxide and then extracted with ether. The ether layer was washed with brine solution, dried and evaporated to yield 0.10 g (51.6%) of **7**, mp 200—205°.

B. From **6a**: In the same manner as described in part A, **6a** afforded **7**, mp 207—210° in 85.5% yield.

C. From **5b**: The same procedure was followed as above except that a reaction time was 70 hr. Usual work-up gave **7** in 51.1% yield.

When the above experiment was conducted using a reaction period of 20 hr, **5a** was obtained in nearly quntitative yield.

D. From **6b**: Compound (**7**) was obtained in 35.2% yield as described in part C. The ether layer that separated from 5% hydrochloric acid layer was dried and evaporated to yield 2′-benzoyl-4′-chloroacetanilide in 34.8% yield.

The IR spectra of the products (**7**) obtained in A—D were identical with that of an authentic sample.[3a)]