

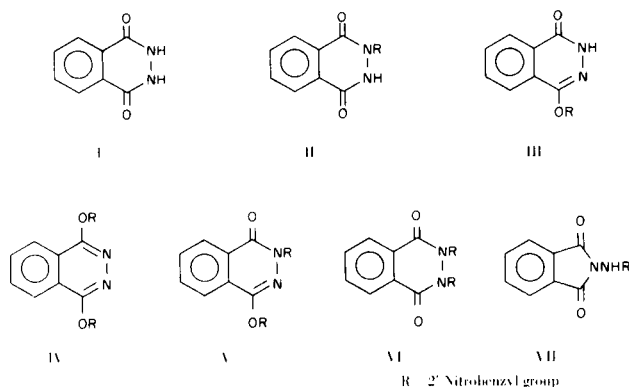
Syntheses of the Heterocyclic Ring Substituted 2'-Nitrobenzylphthalazine-1,4-diones

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We have synthesized and spectrally characterized the five possible heterocyclic ring substituted 2'-nitrobenzylphthalazine-1,4-diones. Selective alkylation of the tautomers of phthalazine-1,4-dione (phthalhydrazide) with 2'-nitrobenzyl chloride furnishes the *O*- and *N*-monoalkyl isomers and the *O,N*-, *O,O*- and *N,N*-dialkyl isomers. These isomers are depicted below along with the parent compound phthalazine-1,4-dione (I) and the *N*-amino-phthalimide derivative (VII), which is isomeric to the monoalkylated compounds.



Both reactions of 2'-nitrobenzylhydrazine with phthalic anhydride in dimethyl sulfoxide, and with phthaloyl chloride (in the presence of pyridine) in tetrahydrofuran furnished II. The isomeric co-product VII, was isolated from reactions of the hydrazine and phthalic anhydride in glacial acetic acid or in dimethyl sulfoxide at temperatures of less than 70°. The hydrazine hydrochloride was isolated and gave a satisfactory analysis. Compound II was the only isolable material from the alkylation of thallos phthalhydrazide by 2'-nitrobenzyl chloride in dimethylformamide.

Alkylation of the monosodium salt of hydrazide I in dimethyl sulfoxide by 2'-nitrobenzyl chloride gave the *O*-alkylated compound III. Both this solvent and benzylating agents have been shown to favor alkylation at the more electronegative atom in ambident nucleophilic systems (2). Further alkylation of the sodium salt of III by

this halide in dimethyl sulfoxide or dimethylformamide produced IV, the *O,O'*-dialkyl material; likewise, alkylation of the salt of II furnished V, the *O,N*-dialkyl material. These results were apparently the consequence of an *O*-directed alkylation effect due to the solvents.

Finally, the series was complete when VI, the *N,N'*-dialkylphthalazine-1,4-dione was isolated after the reaction of *N,N'*-bis-2'-nitrobenzyl hydrazine with phthalic anhydride in dimethyl sulfoxide.

All compounds showed strong and distinct ir (potassium bromide) absorption at the 1530 cm^{-1} and 1320 cm^{-1} regions due to the aryl nitro group. Also characterizing the compounds' ir spectra, was the presence or absence of the phthalazine-1,4-dione heterocyclic ring carbonyl in the 1650 cm^{-1} region. All displayed an identifiable benzylic hydrogen response in nmr spectra run in trifluoroacetic acid, whose solvent power for these compounds was indispensable. Resolution of the benzylic hydrogens of the *O*- and *N*-monoalkylated isomers allowed quantitative analysis of weighed mixtures.

The ir doublet attributable to the phthalimide 5-membered ring at 1790 cm^{-1} and 1750 cm^{-1} distinguished VII from II (3). Also, II recorded a 5.85 ppm hydrogen response; whereas, the phthalimide compound recorded a 5.50 signal. *O*-Monoalkylated III had an N-H stretch at 3200 cm^{-1} indicating that its unsubstituted cyclic amide group was intact. Its benzylic 6.08 ppm response reflected the influence of the more electronegative oxygen atom. As a result of both oxygens being involved in an enolic substitution, the ir of IV revealed the absence of any strong absorption in the carbonyl region; it did record a weak and broad band at 1625 cm^{-1} due to the two equivalent C=N groups. Its benzylic nmr signal was at 6.18 ppm. Compound VI has both carbonyl groups fixed; this structural characteristic caused an enhanced 1670 cm^{-1} absorption. Its benzylic signal was at 6.00 in the nmr, reflecting the diminished deshielding effect exerted by nitrogen as compared to that of oxygen. Compound V gave an interesting nmr spectrum in that two non-equivalent benzylic hydrogens were not observed; however, a response of three distinct hydrogens in a 1:2:1 ratio sug-

gested that one group had two non-equivalent hydrogens. This was attributed to the effect of hydrogen bonding fixing the *N*-substituted benzylic carbon. An effect of this kind is seen in the nmr spectrum of dimethylformamide, where the *N*-methyl groups are fixed in space by the hydrogen bonding of their hydrogens which have two distinct chemical shifts (4).

We have been able to alkylate thallos phthalhydrazide with 2'-nitrobenzyl chloride in dimethylformamide. This reaction furnished material identified by ir and nmr as compound II and is a useful method of preparing II in large amounts.

The acetylated derivatives of II and III share spectral characteristics with acetylated *N*-methylphthalazine-1,4-dione (5). Only one acetyl methyl group is detected in all of their nmr spectra run in DMSO- d_6 . Carbonyl absorption for these acetyl derivatives was at 1750 cm^{-1} in the ir. Since this is the region where the *O*-acetyl carbonyl group of *O,N*-diacetyl phthalazine-1,4-dione absorbs, these compounds are probably acetylated at the oxygen atom of the alternate tautomeric amide group. Acetic anhydride was used for acetylation reactions.

EXPERIMENTAL

All infrared spectra were run on a model 237r Perkin-Elmer spectrophotometer and used potassium bromide pellets which were made with a Wilkes Co. pelletizer. Nmr spectra were obtained on a Varian model A-60A spectrometer at 60 MHz with tetramethylsilane as internal standard. Reactions were carried out under a nitrogen blanket. Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus when the melting point range was recorded under 250° ; above this range a Mel-Temp apparatus was used. Mass spectra molecular ions have been confirmed for all compounds except V. The authors would like to thank the National Science Foundation for grant GP 6926 for the purchase of a Varian A60A spectrometer and the City University of New York for research funds.

2-(2'-Nitrobenzyl)phthalazine-1,4-dione (II).

A solution of 10.26 g. (0.06 mole) of 2'-nitrobenzyl chloride in 50 ml. of tetrahydrofuran was added dropwise to a stirred mixture of 12.0 g. of 85% hydrazine hydrate (0.20 mole of hydrate) in tetrahydrofuran, and stirring was continued for three days at room temperature in a nitrogen atmosphere. Evaporation of the reaction mixture at reduced pressure yielded a brown oil which was dissolved in a diethyl ether-water mixture (150 ml. of each). After separation of the phases, the ether layer was extracted with two additional 50-ml. portions of water which were combined and added to the aqueous layer. Both ether and aqueous phases evaporated to oils with infrared N-H absorption at 3250 cm^{-1} and also at the 1520 cm^{-1} and 1330 cm^{-1} regions (assigned to aryl-nitro group absorption).

The ether layer was dried over magnesium sulfate and evaporated to an oil (3.0 g.). The oil was treated with phthalic anhydride (2.6 g., 0.016 mole) in 100 ml. of dimethyl sulfoxide at 70° for 24 hours, to produce compound VII.

The aqueous phase was evaporated at reduced pressure to a brown oil. The oil was separated from the hydrazine hydrochloride

by dissolving it in chloroform, cooling and filtering. The filtrate was concentrated to an oil (7.05 g., 70%). A sample (1.76 g., 0.01 mole) of crude 2-nitrobenzyl hydrazine was treated with 1.48 g. (0.01 mole) of phthalic anhydride in 100 ml. of dimethyl sulfoxide at $120\text{--}130^\circ$ for 24 hours. The reaction mixture was cooled to room temperature and 100 ml. of water was added to precipitate a gum which was extracted with an ethanol-acetonitrile mixture (200:5 ml.) and thereby converted to a filtrable solid (1.50 g., 50%). Evaporation of the filtrate to one-half its volume gave an additional 0.5 g. (15%) of material. Both solids were purified with no change in their identical infrared spectra; a mixed melting point of the two was undepressed. Several recrystallizations of 0.5 g. of each solid using 175 ml. of a toluene-dimethylformamide mixed solvent (6:1) gave approximately 0.3 g. of identical samples with melting point $276.0\text{--}277.0^\circ$.

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_4$: C, 60.60; H, 3.74; N, 14.15. Found: C, 60.59; H, 3.65; N, 14.08.

Compound II (Alkylation of Thallos Phthalhydrazide).

A 50-ml. solution of thallos ethoxide (24.9 g., 0.10 mole) in anhydrous ethanol was added dropwise to a stirred mixture of phthalhydrazide and 150 ml. of ethanol under nitrogen. Stirring at room temperature was continued for twelve hours and then a 50-ml. solution of 2'-nitrobenzyl chloride (17.1 g., 0.10 mole) in anhydrous ethanol was added in 5-ml. portions. The reaction mixture was refluxed for twenty-four hours and then ethanol was distilled as dimethylformamide was added until the distillate temperature reached 110° . The reaction mixture was stirred at this temperature for ten hours and then filtered at room temperature. A solid residue was washed twice with 50 ml. of ethanol and the washes were added to the reaction filtrate for a combined solution which gave 5 g. of solid (17%) after cooling at -10° for five days. This precipitated material was extracted twice with 20 ml. of acetone and the 4.5 g. residue was almost pure compound II with an infrared spectrum identical to an analytical sample of II prepared above.

The reaction residue contained no additional phthalhydrazide derivative and its acetylation furnished diacetyl phthalhydrazide (obtained by the evaporation of the acetic anhydride reaction filtrate). The residue of the filtered acetylation solution was an inseparable mixture of thallos acetate and thallos chloride which darkened at room conditions and had a broad melting range starting at about 300° .

4-(2'-Nitrobenzyloxy)-2H-phthalazin-1-one (III).

Oil dispersed sodium hydride (1.1 g., 53.5% oil emulsion, 0.025 mole, sodium hydride) was mixed with 75 ml. of petroleum ether ($30\text{--}70^\circ$) in a nitrogen atmosphere. The hydride was allowed to settle and the clear portion of the petroleum ether was removed with a pipet; residual ether, about 10 ml., was removed by use of the rotary evaporator in a $30\text{--}40^\circ$ bath. Dimethyl sulfoxide (200 ml.) was added dropwise onto the hydride while vigorous stirring was maintained. When hydrogen evolution ceased, the reaction flask immersion temperature was slowly raised to 60° and kept at this temperature until no further hydrogen evolution was observed. Phthalhydrazide (4.1 g., 0.025 mole) was added in three batches to the mixture at room temperature. A bright yellow color developed in the mixture which was stirred for forty minutes. Then 2'-nitrobenzyl chloride (4.33 g., 0.025 mole) dissolved in 50 ml. of dimethyl sulfoxide was added dropwise causing a progressive change in color from yellow to a final turbid brown. Stirring was continued for three hours under nitrogen, after which time 75 ml. of water was added and the flocculent mixture was then stirred an additional hour before filtration.

On cooling the filtrate from the reaction mixture, a solid precipitated which weighed 1.30 g. Compound III and sodium chloride were extracted from this solid by a large excess of ethyl ether saturated with water and collected by evaporation on the rotary evaporator. About 0.40 g. of this compound were obtained by extraction of this solid mixture with methanol; a residue of sodium chloride was collected (1.02 g., 70%).

The solid reaction residue was placed in an Abderhalden drying pistol under a toluene reflux and dried at 0.10 mm pressure for one day. This solid was extracted with 100 ml. of refluxing diethyl ether leaving a 3.50 g. residue which was recrystallized from an ethanol-dimethylformamide mixture (3:1) to yield 1.50 g. of pure material. The identical material was obtained by recrystallizing recovered mother-liquor material (1.60 g.) in the same fashion; it also had an m.p. 277.5-278.5°. From the reaction mixture residue and the filtrate about 4.0 g. (53%) of III was collected.

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.60; H, 3.74; N, 14.15. Found: C, 60.60; H, 3.85; N, 14.05.

1,4-Bis(2'-nitrobenzyloxy)phthalazine (IV).

Compound III (7.13 g., 0.024 mole) was mixed in 150 ml. of dimethylformamide with sodium hydride oil emulsion (1.08 g., 53.5%, 0.024 mole) after the emulsion was treated as previously described. During the mixing both a nitrogen atmosphere and a temperature of 100° were maintained, while vigorous stirring was continued for thirty-six hours. A deep blue heterogeneous mixture resulted. Dropwise addition of a solution of the 2'-nitrobenzyl halide (4.68 g., 0.024 mole) in 50 ml. of dimethylformamide caused a gradual change in color to a brown heterogeneous mixture. The reaction was kept at 100° for an additional forty-eight hours with vigorous stirring. Filtration at room temperature yielded sodium chloride which was dried as before to 1.24 g. (88.5%). Evaporation of the filtrate left a solid which was dried at 0.10 mm pressure in an Abderhalden drying pistol heated by refluxing toluene. After extraction with 50 ml. of diethyl ether for twenty-four hours, the crude residue weighed 7.5 g. (72%) and had a melting point of 170.0-200.0°. The ether extract gave an oil whose thin-layer chromatogram showed a mixture of the original halide and the product. After this extraction, the bulk material was recrystallized as follows. A 3.75-g. portion was dissolved in 175 ml. of boiling 3:1 ethanol-dimethylformamide. Three recrystallizations gave an analytical sample with a melting point 273.0-274.0°.

Anal. Calcd. for $C_{22}H_{11}N_4O_6$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.03; H, 3.88; N, 13.03.

2-(2'-Nitrobenzyl)-4-(2'-nitrobenzyloxy)-2H-phthalazin-1-one (V).

Compound II was prepared as indicated. The pure material (3.56 g.) was mixed with an equivalent amount of sodium hydride (1.35 g., 55.35% oil emulsion, 0.02 mole of hydride) which had been treated with petroleum ether as previously described. After the mixture had been left overnight at room temperature with stirring under nitrogen, no evolution of hydrogen was observed; no hydrogen was detected even after the bath was heated to 80° and traces of methanol added.

The salt mixture was then allowed to cool to room temperature and an 2'-nitrobenzyl chloride solution (3.43 g., 0.02 mole in 50 ml. of dimethylformamide) was added dropwise over a period of fifteen minutes. The temperature in the flask was raised to 100° slowly, and stirring was continued for thirty-six hours, after which time the reaction was cooled at -10° for ten hours. The mixture was then allowed to reach room temperature and filtered. Residual

sodium chloride was collected and weighed 0.90 g. (75%). The filtrate was evaporated and the resulting oil was vacuum dried, extracted with 30 ml. of ethanol and then 20 ml. of diethyl ether. A 5.1 g. (60%) solid residue was collected by filtration and the filtrate was evaporated to an oil which weighed 1 g. and could not be solidified. The solid was recrystallized from 200 ml. of ethanol, and then twice from chloroform with decolorization by Norite. The dialkyl compound collected weighed 1 g. and its infrared spectrum was identical to that of the 5.1 g. starting sample. The compound had a melting point of 280.0-281.0°.

Anal. Calcd. for $C_{22}H_{16}N_4O_6$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.92; H, 3.59; N, 13.23.

2,3-Bis(2'-nitrobenzyl)-2H,3H-phthalazine-1,4-dione (VI).

Procedure.

Into a well-stirred solution of hydrazine hydrate (6.00 g. of 85% hydrate, 0.10 mole) in 250 ml. of tetrahydrofuran, was added a 50-ml. solution of 2'-nitrobenzyl chloride (10.26 g., 0.06 mole) in tetrahydrofuran. Addition was completed in fifteen minutes under a nitrogen atmosphere. After fifteen hours of stirring at room temperature, the mixture was chilled at -10° for two hours. An immiscible layer containing hydrazine hydrate and hydrazine hydrochloride (ca. 15 ml.) was separated and the tetrahydrofuran solution was washed twice with 50-ml. portions of saturated aqueous sodium chloride and then dried with 2.5 g. of anhydrous magnesium sulfate. After filtration, the tetrahydrofuran layer was evaporated to an oil on the rotary evaporator with a room-temperature bath which was then slowly raised to 60°.

For reaction with phthaloyl chloride, the oil was dissolved in 250 ml. of tetrahydrofuran and 9.48 g. (0.12 mole) of pyridine was added. While this mixture was kept under nitrogen, a solution of phthaloyl chloride in 50 ml. of tetrahydrofuran was added dropwise; the initial reaction was exothermic. A yellow-orange solid precipitated and was filtered after the reaction mixture had been left at room temperature for twenty-four hours. The filtrate was evaporated to a residue on the rotary evaporator and the residue was extracted with 100 ml. of a 1:1 ethanol-diethyl ether mixture to furnish a crude solid, 3 g. (23%), melting point 220-240°. The solid was partitioned between a mixture of 80 ml. of 0.1 *N* aqueous sodium hydroxide and 60 ml. of chloroform. The aqueous layer was washed with 50 ml. of diethyl ether and then 50 ml. of benzene. All organic washes were combined and concentrated to 50 ml. to which 100 ml. of methanol was added. A solid precipitated (2.5 g.) when the solution was cooled to -10°. A 1.0-g. sample was recrystallized from acetone. The purified material had a melting point 280.5-281.5°.

Anal. Calcd. for $C_{22}H_{16}N_4O_6$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.00; H, 3.80; N, 12.98.

N-Amino-*N'*-(2'-nitrobenzyl)phthalimide (VII).

A sample of 2'-nitrobenzylhydrazine was prepared by treating 12 ml. of 85% hydrazine hydrate with 2'-nitrobenzyl chloride (10.26 g., 0.06 mole). The reaction mixture was stirred at room temperature for four days under nitrogen. An ether layer, obtained as in the procedure describing the preparation of compound II, was evaporated to an oil which, after vacuum drying, weighed 0.96 g. (0.053 mole, 88%). A thin-layer silica-gel chromatogram (in chloroform) of this oil developed with ethanol showed the usual *R_f* 0.90 spot and an insignificant trace of the halide. The oil was treated with phthalic anhydride (7.85 g., 0.053 mole) in dimethyl sulfoxide at 70° for twenty-four hours. Evaporation of the solvent at 60° and 15 mm (rotary evaporator) furnished a dark oil; about 250 ml. of 95% ethanol was mixed with the oil to precipitate

a gum which was collected by filtration.

The gum was dissolved in refluxing 2:1 ethanol-dimethylformamide and was twice decolorized with 0.10 g. of Norite. The precipitate was collected by filtration, extracted successively with 100 ml. of diethyl ether and acetone; the powdery residue was collected and added to the material isolated as described below.

Treatment of the Filtrate from the Precipitated Gum.

This filtrate was evaporated to one-half its volume and mixed with 100 ml. of diethyl ether to precipitate a solid which was collected and combined with the first batch of solid isolated; the combined weight was 4.3 g. (26%). Before recrystallization of this crude mixture, its infrared spectrum showed the phthalimide heterocyclic ring doublet of the imidic carbonyls. Distinct absorption bands of the aryl-nitro group were observable and a weak 1650 cm^{-1} response indicated contamination by a phthalhydrazide derivative. This band was eliminated by two recrystallizations from 2:1 ethanol-dimethylformamide to give 1.80 g. of crystalline material whose nmr in trifluoroacetic acid showed it to be still not pure. This sample was dissolved in 125 ml. of chloroform and decolorized with 0.5 g. of Norite before being passed through a

1-cm diameter column of 5 g. of neutral alumina (Brockman activity I) that had been prewashed with chloroform (150 ml.). The eluent was evaporated to give an oil which solidified in the presence of 15 ml. of glacial acetic acid and 15 ml. of water. The solid was recrystallized twice from ethanol-dimethylformamide and had a melting point $157.0\text{-}158.5^\circ$.

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_4$: C, 60.60; H, 3.74; N, 14.15. Found: C, 60.61; H, 3.47; N, 14.32.

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