More Convenient Syntheses of o-Azidobenzaldehyde and 2-Substituted Indazoles

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Improved syntheses of o-aminobenzaldoxime, o-azidobenzaldehyde, and 2-substituted indazoles are described. An unequivocal synthesis of 2-(2-dimethylaminoethyl)indazole is reported.

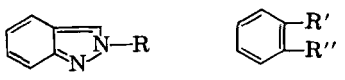
Because a series of 2-substituted indazoles (I) was desired for pharmacological evaluation, synthetic routes to these compounds were investigated. Recently there was reported the synthesis of 2-arylindazoles by the thermal decomposition in polychlorobenzenes of *o*-azidobenzylidene amines (II), which were prepared by condensation of *o*-azidobenzaldehyde (III) with the appropriate amines (1). The preparation of III by nitrous acid treatment of *o*-aminobenzaldoxime (IV) was previously reported by Bamberger and Demuth (2). Although Bamberger readily obtained IV from the aminoaldehyde (V) the synthesis of V from the nitroaldehyde (VI) required voluminous quantities of reactants and solvents. Hence, a route to large quantities of IV was sought.

Hydrogenation of *o*-nitrobenzaldoxime (VII) to IV without concomitant reduction of the oxime function was conveniently effected with 5% palladium-on-carbon in 70% yield.

Although difficulty was initially encountered in converting IV to III, it was found that III could more easily be isolated by extraction rather than by the steam distillation method reported previously (2).

Condensation of III with aniline or 2-dimethylaminoethylamine in dimethylformamide gave the intermediate Schiff base II which was not isolated by being thermally decomposed to the indazole I in refluxing dimethylformamide. This route to I allows the reaction mixture to be poured into water; the product is then easily isolated by filtration or extraction. Hence the use of water-insoluble, nonvolatile polychlorobenzenes is avoided; furthermore, isolation of the Schiff base is unnecessary.

The dimethylaminoethyl derivative (*Ib*), thus obtained, confirmed the structural assignment of Jao and Shchukina (3), who synthesized *Ib* and its 1-substituted isomer by the equivocal method of alkylating indazole with 2-dimethylaminoethyl chloride.



Ia R = C_6H_5
Ib R = $(CH_3)_2N(CH_2)_2$

II R′ = CH=N—R, R″ = N_3
III R′ = CHO R″ = N_3
IV R′ = CH=NOH, R″ = NH_2
V R′ = CHO, R″ = NH_2
VI R′ = CHO, R″ = NO_2
VII R′ = CH=NOH, R″ = NO_2

EXPERIMENTAL[1]

o-Aminobenzaldoxime (IV)—A mixture containing 97 Gm. (0.58 mole) of VII (4), 22 Gm. of 5% palladium-on-carbon (50% moisture), and 1600 ml. of ethanol was stirred with hydrogen at atmospheric pressure for 30 min., the temperature being maintained between 25 and 35° during the hydrogenation. Removal of the catalyst followed by evaporation of the solvent gave the crude product. Recrystallization from toluene gave 63 Gm. (79%) of IV, m.p. 136–136.5° [lit. (2) m.p. 132–133°].

o-Azidobenzaldehyde (III)—To a cooled stirred suspension of 4.08 Gm. (0.03 mole) of IV in 30 ml. of concentrated hydrochloric acid was added a solution of 2.28 Gm. (0.033 mole) of sodium nitrite in 4 ml. of water at 0–5°. To the solution was added 25 ml. of water followed by 60 ml. of 25% aqueous sodium hydroxide at 15–20°. The mixture was stored at room temperature for 16 hr., extracted with ether (3 × 75 ml.), the extracts dried ($MgSO_4$), and concentrated to dryness to give the crude product. Crystallization from hexane gave 2.35 Gm. (53%) of III, m.p. 29–34° [lit. (2) m.p. 35–37°].

2-Phenylindazole (Ia)—A solution of 1.47 Gm. (0.01 mole) of III, 1.03 Gm. (0.011 mole) of aniline, 0.1 Gm. of glacial acetic acid, and 20 ml. of dimethylformamide was stirred at 90–100° for 2 hr. and then refluxed for 30 min. After the mixture was cooled and poured into 400 Gm. of ice water, the product was collected and recrystallized from hexane to give 1.08 Gm. (56%) of *Ia*, m.p. 81–83° [lit. (1) m.p. 82–83°].

2-(2-Dimethylaminoethyl)indazole Dihydrochloride (Ib)—A solution of 3.11 Gm. (0.021 mole) of III, 2.21 Gm. (0.024 mole) of 2-dimethylaminoethylamine, 0.1 Gm. of glacial acetic acid, and 20 ml. of dimethylformamide was stirred at 90–100° for 2 hr. and then refluxed for 45 min. After the mixture was poured into 400 Gm. of ice water, the resulting solution was extracted with ethyl acetate (3 × 100 ml.), the extracts dried ($MgSO_4$), and concentrated to dryness *in vacuo*. Treatment of the free base with methanolic hydrogen chloride gave 2.63 Gm. (48%) of white crystals. Recrystallization from methanol gave the analytical sample, m.p. 181–191° [lit. (3) m.p. 171–181°]; the ultraviolet spectrum was identical to that reported for *Ib* (3).

Anal.—Calcd. for $C_{11}H_{15}N_3 \cdot 2HCl$: C, 50.39; H, 6.54; Cl, 27.04; N, 16.20. Found: C, 50.01; H, 6.63; Cl, 26.89; N, 16.00.

The *picrate* was prepared quantitatively from *Ib* and picric acid in ethanol; m.p. 241–243° dec. [lit. (3) 235° dec.].

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[1] All melting points are corrected. Elemental analyses were performed by Grant Gustin and Marvin Tefft.

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Keyphrases

o-Azidobenzaldehyde—synthesis
2-Substituted indazoles—synthesis
Palladium-on-carbon—hydrogenation
Condensation reactions

Solubilization of Aminopteridines

By MILTON LAPIDUS

Aqueous solutions of a series of aminopteridines (5–10 mg./ml.) stable at physiologic pH's were prepared either by salt formation with hydrochloric acid or by complex formation with 10 percent deoxyribonucleic acid. Deoxyribonucleic acid was superior to ribonucleic acid, crystalline bovine serum albumin, human serum albumin fraction V, or gum acacia in solubilizing 4,7-diamino-2(*p*-chlorophenyl)-*N*-(2-diethylaminoethyl)-6-pteridinecarboxamide at pH 7. Potentiometric titration detected complex formation between deoxyribonucleic acid and the above aminopteridine.

In the course of preparing injectable solutions of a number of aminopteridines it was observed that very few in the series under investigation were appreciably soluble in water. The general lack of aqueous solubility of substituted pteridines has been reported as being due to substituted polar groups (OH, SH, and NH_2) (1). Pteridine (unsubstituted) was reported as being highly soluble (1 part in 7.5 parts of water at 20°).

Although classic salt formation has been used successfully to solubilize aliphatic amines, this method has limited applicability to weakly basic aminopteridines. The apparent acid solubility of triamterene (2,4,7-triamino-6-phenylpteridine) is reversed as the pH is raised to 7 (2).

Complex formation has been reported to increase the aqueous solubility of small molecules (3–5). Speculation that deoxyribonucleic acid, ribonucleic acid, serum proteins, and gum acacia may form aminopteridine complexes with enhanced solubility characteristics stimulated this study.

EXPERIMENTAL

The aminopteridines studied were synthesized by Osdene *et al.* (6, 7). Deoxyribonucleic acid-sodium (DNA-Na), ribonucleic acid-sodium (RNA-Na), and crystalline bovine serum albumin (BSA) were purchased from Nutritional Biochemical Corp., Cleveland, Ohio; human serum albumin (HA) fraction V from Pentex, Inc., Kankakee, Ill.; and USP gum acacia from S. B. Penick and Co., New York, N. Y. The standard reagents used were the best grades commercially available.

Analysis of Wy-4029—Wy-4029 [4,7-diamino-2-(*p* - chlorophenyl) - *N* - (2 - diethylaminoethyl) - 6-pteridinecarboxamide] in 0.1 *N* sulfuric acid fluoresces at 445 mμ when activated at 390 mμ. Using the Aminco Bowman spectrophotofluorometer, a linear response was obtained in the concentration range of 2–9 mcg./ml.

pH of Complete Solubility and Solubility Reversal—To 25 mg. of each of the aminopteridines suspended in 50 ml. of water increments of 1 *N* HCl were added until the soluble end point was reached. The pH was monitored with a Beckman pH meter, and pH equilibrium was established after the addition of each increment of acid. Back titration with 0.1 *N* sodium hydroxide resulted in the end point of solubility reversal.

pH Solubility Profile of Wy-4029—To a series of 500-mg. samples of Wy-4029 suspended in 20 ml. of water were added varying amounts of concentrated hydrochloric acid to obtain a constant pH of 3, 4, 5, 6, or 7. The contents of each beaker was stirred for 1 hr. at 25°. The mixtures were then filtered through a 0.45-μ Millipore filter (the standard method subsequently used) and the concentration of Wy-4029 in the filtrate was determined.

Potentiometric Evidence of Complex Formation—Solutions of Wy-4029 (50 mg./100 ml.), DNA-Na (1 Gm./100 ml.), and Wy-4029 (50 mg./100 ml.) plus DNA-Na (1 Gm./100 ml.) were adjusted to pH 3.5 with 1 *N* hydrochloric acid and titrated with 0.1 *N* sodium hydroxide, pH equilibrium being established after each addition of alkali.

Stability of Macromolecule–Aminopteridine Complex—To 25 mg. of each of the aminopteridines was added 50 ml. of a 1% solution of DNA-Na (pH 2.5), and the mixtures were triturated in a Potter-Elvehjem homogenizer until soluble (5 min.). Increments of 0.1 *N* sodium hydroxide were slowly added, pH equilibrium being established after the addition of each increment. The pH at which turbidity occurred was considered the end point of solubility reversal.

Effect of Concentration and pH of Macromolecules on Wy-4029 Solubility—To various concentrations of DNA-Na (pH 5.0), RNA-Na (pH 2.8), HA (pH 4.9), BSA (pH 5.1), and USP gum acacia (pH 4.4) in 20 ml. of water was added an excess (50–400 mg.) of Wy-4029. The mixtures were

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