# Quinazolines and 1,4-Benzodiazepines. XXI.[1] The Nitration of 1,3,4,5-Tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-ones

R. IAN FRYER, J. V. EARLEY, AND L. H. STERNBACH

*Department of Chemical Research, Research Division, Hoffmann-La Roche, Inc., Nutley, New Jersey*

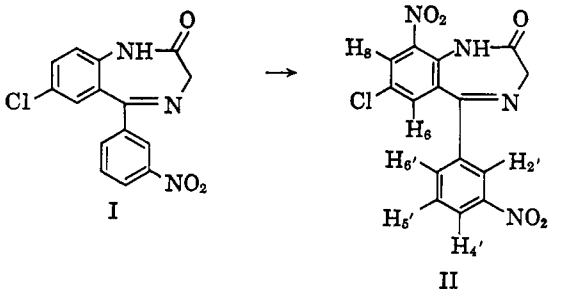
*Received October 1, 1964*

The products obtained by nitration of 1,3,4,5-tetrahydro-5-phenyl-1,4-benzodiazepin-2-ones were unequivocally shown to be tetrahydro-5-nitrophenyl-1,4-benzodiazepin-2-ones and not the expected 7-nitro-1,3,4,5-tetrahydro-5-phenyl derivatives. The orientation of aromatic substituents in the nitration products obtained from various types of 5-phenyl-1,4-benzodiazepin-2-ones is discussed.

It was reported earlier that the nitration of the 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one compounds with potassium nitrate in cold concentrated sulfuric acid led to 7-nitro derivatives[2] and that, under the same conditions, 7-substituted 1,3 dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one compounds were nitrated in the *meta* position of the 5-phenyl substituent.[3]

As a continuation of work in this area we have now investigated the further nitration of one of these compounds, 7-chloro-1,3-dihydro-5-(3-nitrophenyl)-2H-1,4-benzodiazepin-2-one (I), and the nitration products of the two 1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-ones VIa and VIb.[4]

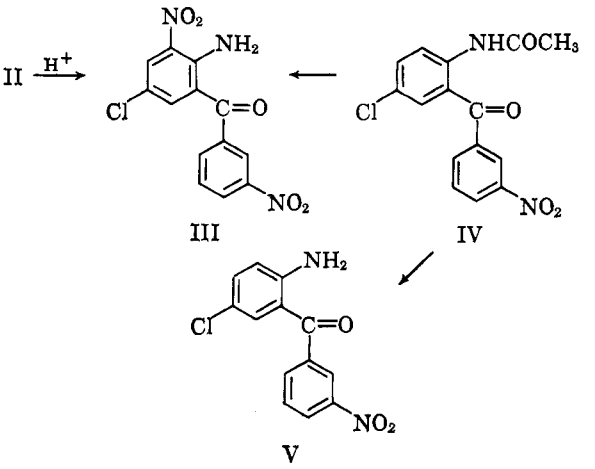
Under the conditions described above, we obtained from I a dinitro compound to which we assign the structure II, a 9-nitro derivative. The position of the second nitro group was determined from an interpretation of the splitting pattern and coupling constants for the aromatic protons in the n.m.r. spectrum. The only orientation of aromatic substituents which was compatible with the observed data was that shown in II.




This highly substituted benzodiazepinone was readily hydrolyzed by acid to the ketone III. Nitration of the acetyl derivative IV of the known ketone V[3] also gave III, the acetyl group presumably being hydrolyzed during work-up.

The nitration of VIa and VIb using potassium nitrate in concentrated sulfuric acid no longer gave appreciable yields of the desired products and a stronger reagent, fuming nitric acid in concentrated sulfuric acid, was required to effect nitration.

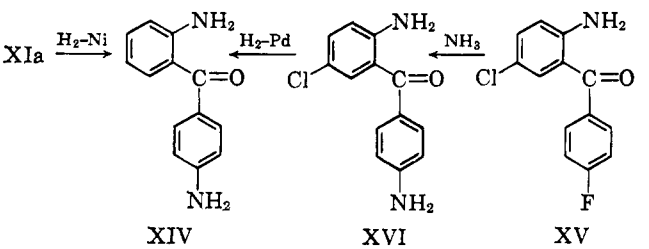
We were surprised to observe that, unlike the 1,3-dihydrobenzodiazepinones, nitration of the 1,3,4,5-tetrahydro compounds gave, as the major products,




derivatives nitrated in the 5-phenyl substituent. Nitration of VIb gave one product, VIIIb,[5] isolated in 81% yield, while from VIa the two mononitro derivatives VIIa[5] and VIIIa[5] were obtained and isolated in 48 and 23% yield, respectively.

Oxidation of these three products with chromium trioxide in glacial acetic acid gave the unsaturated 1,3-dihydro compounds IXa, Xa, and Xb, respectively. These benzodiazepinones were then hydrolyzed to the aminonitrobenzophenones XIa, XIIa, and XIIb. (See Scheme I).

2-Amino-3'-nitrobenzophenone (XIIa) was identified and compared with an authentic sample.[6] The previously unknown 2-amino-4'-nitrobenzophenone (XIa) was reduced with hydrogen and Raney nickel to the known 2,4'-diaminobenzophenone (XIV).[7] This sub-




stance (XIV) was then identified with an authentic sample which was prepared by causing 2-amino-5-chloro-4'-fluorobenzophenone (XV) to react with ammonia under pressure, and subsequent dehalogenation of the product XVI with hydrogen in the presence of a palladium catalyst.

(1) Paper XX: W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **29**, 1621 (1964).

(2) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(3) R. Ian Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 4977 (1963).

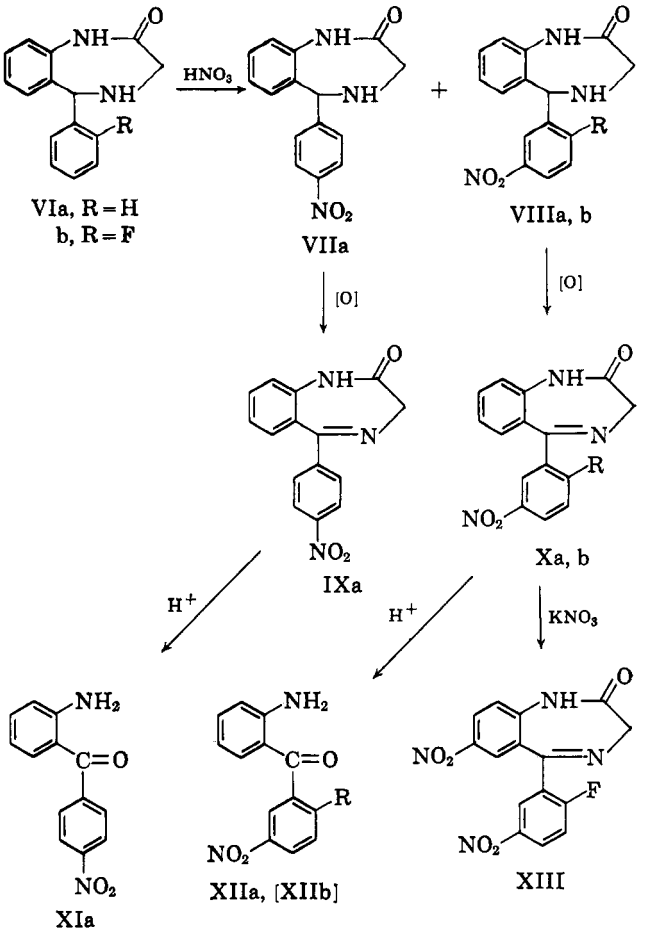
(4) R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).

(5) For convenience and simplicity, the compounds described throughout the discussions will be referred to by their correct structures.

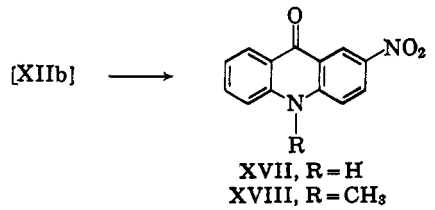
(6) D. F. DeTar and D. I. Relyea, *J. Am. Chem. Soc.*, **76**, 1680 (1954).

(7) E. Haase and E. Moyat, *Ann.*, **283**, 171 (1894).

SCHEME I




2-Amino-2′-fluoro-5′-nitrobenzophenone (XIIb) was not isolated. It cyclized spontaneously to the known acridone XVII (m.p. >350°)[8] during the hydrolysis reaction.[9] The acridone was converted by literature, methods[8] to the known N-methylacridone XVIII (m.p. 276°) which was compared with an authentic sample prepared as reported in the literature.[8] Additional evidence for the 5-(2-fluoro-5-nitrophenyl)-benzodiazepinone structures VIIIb and Xb was obtained by the nitration of Xb with potassium nitrate in cold concentrated sulfuric acid to the known dinitrobenzodiazepinone XIII.[2]




XVII, R=H
XVIII, R=CH3

The orientation of the entering group in the nitration of 1,3-dihydro-5-phenyl-1,4-benzodiazepin-2-ones[2,3] appears to follow the usual substituent effects for electrophilic aromatic substitution. The strong *para*-directing influence of the acylamino group is well known and the formation of 7-nitro derivatives[2] is readily rationalized on this basis. The formation of 5-(3-nitrophenyl) compounds from 7-substituted 1,3-dihydro-5-phenylbenzodiazepinones[3] is not unexpected although less predictable than in the previous case. Depending upon the relative decrease in reactivity of the aromatic part of the benzodiazepinone nucleus, electrophilic substitution would be expected to give either a 9-nitro or a 5-(3-nitrophenyl) derivative. When the 7-substituent is chlorine (less deactivating than nitro) 9-nitration does occur but only subsequent to the introduction of the first nitro group on the 5-phenyl substituent.

The fact that, irrespective of the presence or absence of a substituent in the 7-position of 1,3,4,5-tetrahydro-5-phenyl-1,4-benzodiazepin-2-ones, we obtained only 5-(nitrophenyl) derivatives would appear to be an anomaly. The orientation of the substituents in the 5-phenyl ring itself is however not surprising. In the case of VIb, the results obtained conform with the known strong *para*-directing influence of fluorine, while in VIa the results conform with the known fact that benzylamine and substituted benzylamines give predominately mixtures of *meta* and *para* isomers.[10]

This anomaly appears to exist then in the fact that substitution takes place in the 5-phenyl ring and not in the 7-position, as would be predicted by the additive influence of the aminomethylene and acylamino substituents on the aromatic ring of the benzodiazepinone nucleus.

## Experimental

All melting points were determined microscopically on a hot stage and were corrected. Infrared spectra were determined with a 3% chloroform solution or in a potassium bromide pellet. N.m.r. spectra were determined in deuterated dimethyl sulfoxide solutions on a Varian A-60 spectrometer using tetramethylsilane as the reference standard.

**7-Chloro-1,3-dihydro-9-nitro-5-(3-nitrophenyl)-2H-1,4-benzodiazepin-2-one (II).**—A solution of 15 g. (0.0554 mole) of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one[11] in 50 ml. of concentrated sulfuric acid was treated at 0° with a solution of 11.25 g. (0.116 mole) of potassium nitrate in 55 ml. of concentrated sulfuric acid. The mixture was stirred for 18 hr. at room temperature, cooled to 0°, and neutralized (pH 8) at that temperature with ammonium hydroxide solution. The solution was filtered and the precipitate was washed well with water and then dissolved in dichloromethane. Starting material was removed by filtering the solution over a small quantity of neutral alumina. Solvent was removed to give 9.1 g. of an oil which was chromatographed over 100–200-mesh silica using ether as the eluent. Removal of solvent gave 4.4 g. of the product as a crystalline solid, which on recrystallization from a dichloromethane–methanol mixture gave 3.5 g. (20%) of the pure dinitrobenzodiazepinone as pale yellow prisms, m.p. 164–167°. The n.m.r. spectrum showed the three protons *ortho* to the nitro groups (2′-H, 4′-H, 8-H) overlap at $\tau$ 1.57–1.73. 6′-H appears at $\tau$ 2.08 ($J_{5',6'}$ = 7.8 c.p.s., $J_{2',6'} + J_{4',6'}$ = 3.3 c.p.s.), 5′-H at 2.37 ($J_{5',6'}$ = 7.8 c.p.s., $J_{4',5'}$ = 8.5 c.p.s.), and 6-H at 2.45 ($J_{6,8}$ = 2.4 c.p.s.).

*Anal.* Calcd. for $C_{15}H_9ClN_4O_5$: C, 49.95; H, 2.51. Found: C, 50.09; H, 2.72.

**2-Amino-5-chloro-3,3′-dinitrobenzophenone (III). A.**—A mixture of 0.5 g. of II, 5 ml. of 3 *N* hydrochloric acid, and 5 ml. of ethanol was heated under reflux for 16 hr. The solution was cooled, made basic with ammonium hydroxide, and extracted with dichloromethane. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated to give, after recrystallization from methanol, 0.35 g. (78%) of III, as bright orange needles, m.p. 156–158°.

*Anal.* Calcd. for $C_{13}H_8ClN_3O_5$: C, 48.54; H, 2.51. Found: C, 48.82; H, 2.83.

(8) K. Lehmstedt and H. Hundertmark, *Ber.*, **64**, 2381 (1931).

(9) See R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc.*, 4979 (1963), for similar cyclizations.

(10) F. R. Goss, C. K. Ingold, and I. S. Wilson, *ibid.*, 2440 (1926).

(11) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

**B.**—A mixture of 0.5 g. of 2-amino-5-chloro-3′-nitrobenzophenone (V),[3] 0.4 g. of potassium acetate, and 5.0 ml. of acetic anhydride was allowed to stand at room temperature overnight. The reaction mixture was dissolved in 25 ml. of dichloromethane which was washed with water, sodium carbonate solution, and then again with water. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated to a colorless oil. Crystallization from an acetone–hexane mixture afforded 0.4 g. (66%) of 4′-chloro-2′-(3-nitrobenzoyl)acetanilide (IV) as pale yellow needles, m.p. 143–145°.

*Anal.* Calcd. for $C_{15}H_{11}ClN_2O_4$: C, 56.53; H, 3.48. Found: C, 56.69; H, 3.49.

A solution of 0.4 g. (1.27 mmoles) of IV in 7 ml. of cold concentrated sulfuric acid was nitrated, using a solution of 0.13 g. (1.3 mmoles) of potassium nitrate in 5 ml. of concentrated sulfuric acid, and worked up as described for II above to give, after recrystallization from methanol, 0.3 g. (75%) of III, m.p. 156–157°.

**1,3,4,5-Tetrahydro-5-(4-nitrophenyl)-2H-1,4-benzodiazepin-2-one (VIIa) and 1,3,4,5-Tetrahydro-5-(3-nitrophenyl)-2H-1,4-benzodiazepin-2-one (VIIIa).**—A solution of 9.5 g. (0.04 mole) of VIa[4] in 35 ml. of concentrated sulfuric acid was cooled to approximately −30° in a Dry Ice–acetone bath. A solution of 2.9 g. (0.042 mole) of 90% nitric acid in 7 ml. of concentrated sulfuric acid was added slowly, keeping the temperature constant. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solution was cooled to −10° and treated at this temperature with ammonium hydroxide to pH 8. The products were extracted into dichloromethane, which was washed, dried, and evaporated.

Crystallization of the residue from methanol gave 4.5 g. of VIIa, as white needles, m.p. 235–237°.

*Anal.* Calcd. for $C_{15}H_{12}N_3O_3$: C, 63.59; H, 4.63. Found: C, 63.44; H, 4.54.

The mother liquors were concentrated and the residue was recrystallized from an acetone–hexane mixture to give 2.2 g. of VIIIa as white needles, m.p. 158–160°.

*Anal.* Calcd. for $C_{15}H_{12}N_3O_3$: C, 63.59; H, 4.63. Found: C, 63.59; H, 5.16.

Fractional crystallization of the mother liquors from an acetone–hexane mixture gave an additional 0.9 g. of VIIa and 0.4 g. of VIIIa, representing combined yields of 48 and 23%, respectively.

**1,3,4,5-Tetrahydro-5-(2-fluoro-5-nitrophenyl)-2H-1,4-benzodiazepin-2-one (VIIIb).**—A mixture of 7.5 ml. of 90% nitric acid and 20 ml. of concentrated sulfuric acid was added dropwise to a cooled (−20 to −30°) solution of 41 g. (0.16 mole) of 1,3,4,-5-tetrahydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one[4] in 300 ml. of concentrated sulfuric acid. The resulting solution was stirred 90 min. and allowed to warm to −5° and was then made basic (pH 8) at that temperature with ammonium hydroxide. The precipitate was obtained by filtration, washed with water, and dissolved in 250 ml. of dichloromethane. The solution was washed, dried, treated with decolorizing carbon, filtered, and concentrated. The product was recrystallized from an acetone–petroleum ether (b.p. 30–60°) mixture to give 38.9 g. (81%) of VIIIb as white needles, m.p. 188–189°.

*Anal.* Calcd. for $C_{15}H_{12}FN_3O_3$: C, 59.80; H, 4.01. Found: C, 59.76; H, 4.00.

**1,3-Dihydro-5-(4-nitrophenyl)-2H-1,4-benzodiazepin-2-one (IXa), 1,3-Dihydro-5-(3-nitrophenyl)-2H-1,4-benzodiazepin-2-one (Xa), and 1,3-Dihydro-5-(2-fluoro-5-nitrophenyl)-2H-1,4-benzodiazepin-2-one (Xb).**—A solution of 0.01 mole of the tetrahydro compound (either VIIa, VIIIb, or VIIIa) in 200 ml. of glacial acetic acid was oxidized at room temperature with a solution of 0.075 mole of chromium trioxide in 2 ml. of water. The mixture was allowed to stand for 17 hr., diluted with water (0°), and made basic (pH 8) with ammonium hydroxide. The product was extracted into dichloromethane, which was washed, dried, filtered, and evaporated. The residue was recrystallized from methanol to give, from VIIIa, 26.6% of Xa as white plates, m.p. 224–227°.

*Anal.* Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94. Found: C, 63.88; H, 4.15.

IXa (25%) was obtained from VIIa as pale yellow prisms, m.p. 279–281°.

*Anal.* Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94. Found: C, 64.32; H, 3.99.

Xb (38%) was obtained from VIIIb as colorless prisms, m.p. 219–222°.

*Anal.* Calcd. for $C_{15}H_{10}FN_3O_3$: C, 60.20; H, 3.37. Found: C, 59.88; H, 3.42.

**2-Amino-4′-nitrobenzophenone (XIa).**—A solution of 0.5 g. (0.018 mole) of IXa in 300 ml. of 6 *N* hydrochloric acid and 300 ml. of ethanol was heated under reflux for 17 hr. The mixture was cooled and neutralized with ammonium hydroxide. The product was extracted into dichloromethane, which was washed, dried, and evaporated. Recrystallization of the residue from a dichloromethane–hexane mixture gave 0.2 g. (41.5%) of the pure compound as orange needles, m.p. 155–157°.

*Anal.* Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16. Found: C, 64.21; H, 3.88.

**2,4′-Diaminobenzophenone (XIV). Method A.**—A suspension of Raney nickel (2 g. wet wt.) in a solution of 0.28 g. (1.16 mmoles) of XIa in 90 ml. of ethanol was hydrogenated to completion [84 ml. of hydrogen adsorbed (3.48 mmoles)]. The catalyst was removed by filtration and the solvent was evaporated. The product was purified by preparing the hydrochloride, which was recrystallized from an acetone–ether mixture, m.p. 170–190° dec. Liberation of the base gave, after recrystallization from an ether–hexane mixture, 40 mg. (16.5%) of product, m.p. 127–129° (lit.[4] m.p. 128–129°).

**Method B.**—A solution of 10 g. (0.04 mole) of 2-amino-5-chloro-4′-fluorobenzophenone[12] (XV) in 200 ml. of ethanol was autoclaved with ammonia at 150° for 24 hr. The resulting solution was evaporated and the residue was extracted with several portions of boiling hexane. By concentrating the hexane fractions and allowing the solution to cool, 8.0 g. of starting material was recovered. Recrystallization of the hexane-insoluble residue from a dichloromethane–hexane mixture gave 1.5 g. of 5-chloro-2,4′-diaminobenzophenone (XVI) as yellow needles, m.p. 152–155°.

*Anal.* Calcd. for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.52; H, 4.79; N, 11.28.

A mixture of 0.5 g. (2 mmoles) of XVI, 0.1 g. of charcoal, 0.3 g. of potassium acetate, 0.1 ml. of 20% palladium chloride, and 0.05 g. of 10% palladium on charcoal was added to 25 ml. of tetrahydrofuran and hydrogenated to completion[13] (theory, 53 ml. of hydrogen, uptake 57 ml.). The catalyst was removed by filtration and the solvent was evaporated. The residue was dissolved in dichloromethane and filtered over 10 g. of grade I, neutral alumina (Woelm). Using ethyl acetate as an eluent, 150 mg. (35%) of pure XIV was obtained, m.p. 126–128°.

**2-Amino-3′-nitrobenzophenone (XIIa).**—A solution of 0.1 g. (0.356 mmole) of Xa in 50 ml. of ethanol and 50 ml. of 6 *N* hydrochloric acid was refluxed and worked up as described for XIa to give, after recrystallization from an ether–petroleum ether mixture, 50 mg. (58%) of pure 2-amino-3′-nitrobenzophenone, m.p. and m.m.p. 91–93° with an authentic sample[6].

**2-Nitro-9-acridanone (XVII).**—A solution of 2.0 g. (6.6 mmoles) of Xb in 25 ml. of 3 *N* hydrochloric acid and 25 ml. of ethanol was refluxed for 17 hr. The mixture was cooled and the product separated by filtration. The precipitate was washed with ethanol and dried to give 1.42 g. (90%) of 2-nitro-9-acridanone as yellow needles, m.p. >350°. The infrared spectrum of this compound was identical with that of an authentic sample.[8]

**1,3-Dihydro-5-(2-fluoro-5-nitrophenyl)-7-nitro-2H-1,4-benzodiazepin-2-one (XIII).**—A solution of 0.5 g. (4.8 mmoles) of potassium nitrate in 1 ml. of concentrated sulfuric acid was added dropwise to a cold (0°) solution of 1.2 g. (4 mmoles) of Xb in 2 ml. of concentrated sulfuric acid. The mixture was kept at room temperature for 18 hr., cooled to 0°, and made basic (pH 8) with ammonium hydroxide. Filtration of the mixture gave the crude product, which was washed with water and dichloromethane. Recrystallization from acetone gave 800 mg. (57%) of pure XIII as white prisms, m.p. and m.m.p. 295–298° with an authentic sample[2].

**Acknowledgment.**—We wish to thank Dr. Floie Vane for the determination and the interpretation of the n.m.r. spectra. We are also indebted to Mr. S. Traiman for the infrared spectra, to Dr. Al Steyermark and his staff for microanalyses, and to Mrs. Nancy Ferrante for valuable technical assistance.

(12) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.* **27**, 3781 (1962).

(13) Method of G. Chase, L. A. Dolan, and D. Wagner, South African Patent 62/3627, assigned to Hoffmann-La Roche (Derwent Publication No. 00006467, Jan. 23, 1963).