

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Reduction of 6,7-Diphenyldibenzo[*e,g*][1,4]diazocine. An Unusual Nucleophilic Aromatic Substitution¹

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Treatment of the title compound (I) with most common reducing agents led to no reaction. When I was allowed to react with excess lithium aluminum hydride in boiling tetrahydrofuran for several hours, *N*-desylcarbazole (II) was isolated in 63% yield. A mechanism is proposed for the reaction which involves a nucleophilic aromatic substitution.

Täuber³ prepared 6,7-diphenyldibenzo[*e,g*][1,4]-diazocine (I) by heating 2,2'-diaminobiphenyl with benzil at 170°. We have confirmed this synthesis, and have also found that I may be more conveniently prepared by heating the same components in acetic acid. Upon acid hydrolysis the compound gave a 95% yield of benzil. The infrared spectrum of I showed no N-H stretching band, and the structure of the compound appears to be firmly established.

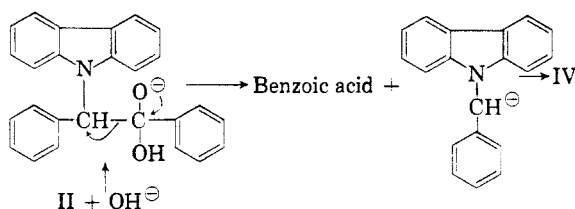
Compound I upon reduction with sodium amalgam in ethanol was reported³ to yield 5,6,7,8-tetrahydro-6,7-diphenyl[*e,g*][1,4]diazocine (III). Täuber established the structure of III by carbon-hydrogen analysis, and by formation of a diacetyl derivative.⁴ As further support for the structure assigned to III additional information has been obtained. Compound III gave the correct analysis for nitrogen, and it showed strong N-H stretching bands at 2.92 and 3.00 μ . The diacetyl derivative showed a carbonyl band at 5.98 μ .

Compound I is rather resistant to reduction, and was unaffected by low pressure catalytic hydrogenation with platinum oxide, or by treatment with zinc and alkali, sodium borohydride, stannous chloride, or lithium aluminum hydride in ether.

When reduction of I was carried out with lithium aluminum hydride in refluxing tetrahydrofuran for 12 hr. under a nitrogen atmosphere, a colorless crystalline substance was isolated which was identified as *N*-desylcarbazole (II). The structural assignment was indicated by elemental analysis and molecular weight. The infrared spectrum showed no N-H stretching band, but did show a carbonyl band at 5.85 μ (chloroform), about 0.1 μ lower than expected for an acetophenone. By way of analogy it was found that a synthetic sample of ethyl 9-carbazoleacetate, prepared according to Seka,⁵ showed the ester carbonyl band at 5.55 μ as compared to 5.75 μ for ethyl acetate. No carbonyl

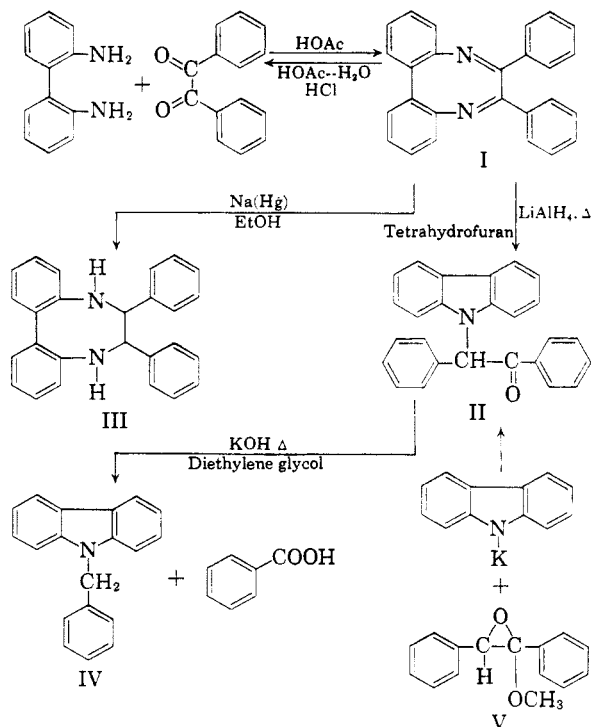
derivatives of II were obtained by conventional methods.

The structure of compound II was established by degradation with potassium hydroxide in diethylene glycol. The cleavage that was expected⁶ to take place was:



Compound IV and benzoic acid were isolated in yields of 45% and 33%, respectively.

It also seemed desirable to synthesize II by an unambiguous method. Attempts to condense carbazole, or various of its salts, with desyl chloride were unsuccessful. Compound II was obtained



(1) Supported in part by a research grant from the National Science Foundation.

(2) National Science Foundation Predoctoral Fellow, 1956-1959.

(3) E. Täuber, *Ber.*, **25**, 3287 (1892).

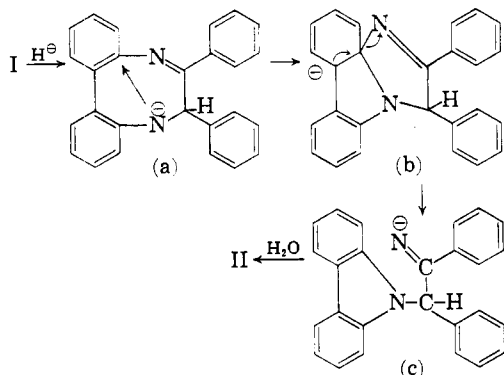
(4) E. Täuber, *Ber.*, **26**, 1703 (1893).

(5) R. Seka, *Ber.*, **57**, 1527 (1924).

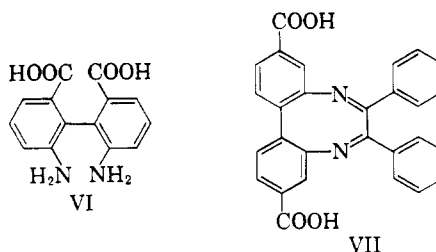
(6) D. J. Cram, J. Allinger, and A. Langemann, *Chem. & Ind. (London)*, 919 (1955).

in 21% yield by the condensation of the potassium salt of carbazole with 1,2-diphenyl-1-methoxy-1,2-epoxyethane (V).⁷

A reasonable mechanism by which compound II may have been formed from I would have the reaction initiated by attack of hydride at one of the azomethine carbons, which would yield (a). Nucleophilic attack by the amide ion on the phenyl ring would lead through (b) to (c). If no further reaction occurred, (c) would after hydrolysis yield



compound II. Ordinarily a ketimine would be expected to be reduced by lithium aluminum hydride to an amine.⁸ No amine was detected in the present work, but a considerable amount of the starting material was not accounted for. The failure of II to form carbonyl derivatives under ordinary conditions suggests that this reduction may be slow, or the solubility of the salt (c) may be quite low. The solubility question is difficult to answer as the reaction is heterogeneous throughout. In structure (b), one phenyl is twisted out of the plane of the other one by an appreciable amount, yet considerable charge delocalization may still occur. This part of the reaction has an analogy in the formation of carbazole from compound VI by heating with barium oxide.⁹ The structure (b) corresponds to what is normally an intermediate in nucleophilic substitution of "activated" aromatic rings.¹⁰ It is not clear whether in this case it is an intermediate or a transition state, since the ring structure of (b) must be under some strain. Compound I probably has the eight-membered ring in a tub form, as does the formally analogous cyclooctratetraene.¹¹ The two rings of the biphenyl grouping are not expected to be co-planar, and in support of this geometry compound VII has been resolved into optical isomers.¹² Thus, no appreciable loss in conjugation is necessitated by the



formation of the multiplanar structure (b). The stabilization of charge afforded by (b) would not, however, be expected to be as great as that of an *ortho*-nitro group in the simple cases.

EXPERIMENTAL

6,7-Diphenyldibenzo[*e,g*][1,4]diazocine (I). A solution containing 5.0 g. of 2,2'-diaminobiphenyl¹³ (prepared from the corresponding dinitro compound¹⁴ by reduction with tin and hydrochloric acid) in 25 ml. of hot acetic acid was added to 5.76 g. of benzil in 110 ml. of hot acetic acid. The resulting solution was heated under reflux for 19 hr., and was then allowed to stand for 24 hr. The crystals were collected, and after recrystallization from acetic acid were obtained as yellow needles, m.p. 236–237° (literature,³ m.p. 238°) wt., 7.0 g. (72%). The ultraviolet spectrum showed λ_{max} 251, ϵ 32,950 and λ_{max} 338, ϵ 2,950 (95% ethanol).

Hydrolysis of compound I. One gram of I was suspended in a solution of 25 ml. of 5*N* hydrochloric acid in 50 ml. of acetic acid. The mixture was heated under reflux in a nitrogen atmosphere for 46 hr. The solution was diluted with water, and the yellow solid was collected, m.p. 95.5–96.5°, wt. 0.56 g. (95%). No mixture melting point depression was observed with an authentic sample of benzil. The hydrolysis of I to benzil and 2,2'-diaminobiphenyl was reported by Täuber,⁴ but no details or yields were given.

The action of various reducing agents on compound I. The compound proved to be rather inert to a number of common reducing agents. By appropriate isolation procedures, the bulk of the material was recovered unchanged after treatment with excess of the following reagents: sodium in ethanol, stannous chloride and hydrochloric acid, lithium aluminum hydride in ether at reflux for 2 hr., lithium aluminum hydride in tetrahydrofuran at room temperature for 72 hr., sodium borohydride in tetrahydrofuran at reflux for two days, catalytic hydrogenation with platinum oxide in tetrahydrofuran, and zinc dust in alcoholic potassium hydroxide. With tin and hydrochloric acid there was obtained a nitrogen free material, m.p. 56–76°, which was not further examined, and which probably resulted from the cleavage of I to give benzil followed by further reaction of the latter.

5,6,7,8-Tetrahydro-6,7-diphenyldibenzo[*e,g*][1,4]diazocine (III). With sodium amalgam in ethanol compound I was reduced to III, colorless, lustrous, granular crystals, m.p. 155–155.5° (reported,³ m.p. 154°). The ultraviolet spectrum showed maxima at 282 and 323 $m\mu$, with ϵ 1150 and 2500 (95% ethanol).

Anal. Calcd. for $C_{20}H_{22}N_2$: N, 7.73. Found: N, 7.89.

***N*-Desylcarbazole (II) from I.** A solution of 2.0 g. of I in 200 ml. of anhydrous tetrahydrofuran was added during 1 hr. to a suspension of 5.0 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran with stirring under an atmosphere of nitrogen. The resulting mixture was then heated under reflux with stirring for 18 hr. After cooling the solution, ethanol was added until the yellow color disappeared, and then water was added until the decomposition was complete. The inorganic material was removed by filtration and washed

(13) S. von Nientowski, *Ber.*, **34**, 3325 (1901).

(14) R. C. Fuson and E. A. Cleveland, *Org. Syntheses, Coll. Vol. III*, 339 (1955).

(7) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *J. Am. Chem. Soc.*, **75**, 3977 (1953).

(8) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956, p. 795.

(9) J. Schmidt and A. Kämpf, *Ber.*, **36**, 3745 (1903).

(10) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).

(11) I. L. Karle, *J. Chem. Phys.*, **20**, 65 (1952).

(12) F. Bell, *J. Chem. Soc.*, 1527 (1952).

with tetrahydrofuran. The combined filtrates were dried with magnesium sulfate and the solvent was removed. The residue was twice crystallized from aqueous acetic acid and yielded light yellow plates, m.p. 181–182.5°, wt. 1.07 g. The inorganic salts were dissolved in dilute hydrochloric acid, combined with the acetic acid filtrates above, and the solution was extracted with chloroform. After drying the extracts the chloroform was evaporated. The residue was twice crystallized from acetic acid and gave pale yellow plates, m.p. 180.5–182.6°, wt. 0.20 g., plus filtrates (A). The total yield of pure *N*-desylcarbazole was 1.27 g. (63%). An analytical sample was prepared by recrystallizing this material first from aqueous acetic acid, and then from a mixture of tetrahydrofuran and hexane, and was obtained as colorless needles, m.p. 184–184.5°. The infrared spectrum in chloroform showed a strong band at 5.85 μ .

Anal. Calcd. for C₂₆H₁₉NO: C, 86.41; H, 5.30; N, 3.88; mol. wt., 361. Found: C, 86.29; H, 5.45; N, 3.93; mol. wt., (Rast) 342.

Filtrates (A) were neutralized with potassium hydroxide and the solution was extracted with chloroform. The chloroform extracts were dried, the solvent was evaporated, and the residue was chromatographed on alumina with chloroform-hexane. There was thus obtained 55 mg. (4%) of *N*-benzylcarbazole (IV) which was identified by mixture melting point and infrared comparison with an authentic sample.

Degradation of N-desylcarbazole. *N*-Desylcarbazole (II), 0.71 g., was dissolved in 40 ml. of diethylene glycol containing 0.11 g. of potassium hydroxide, and the resulting solution was heated under reflux for 3.5 hr. under an atmosphere of nitrogen. The cooled solution was diluted with water and the precipitated solid was collected and washed with water.

The dried solid was crystallized from petroleum ether at 0°, and gave colorless needles, m.p. 117–118°, wt. 0.23 g. (45%). This material gave no melting point depression

(15) N. P. Buu-Hoi and R. Royer, *J. Org. Chem.*, 16, 1198 (1951).

with an authentic sample of *N*-benzylcarbazole (IV) (prepared according to Buu-Hoi and Royer¹⁵). The two samples also gave identical infrared spectra.

The aqueous filtrate from above was acidified and extracted with ether. The ether solution was extracted with *N* sodium hydroxide solution, and the latter was acidified and extracted with ether. The ethereal solution was dried and the solvent was evaporated which yielded a light brown crystalline solid. The solid was recrystallized from water (Norit), m.p. 122–123°. A mixture melting point with benzoic acid (m.p. 122–124°) was 123–124°. The infrared spectra of the isolated solid and benzoic acid were identical. The yield was 0.08 g. (33%).

N-Desylcarbazole (II). Several unsuccessful attempts were made to prepare this compound from carbazole itself, and from its salts as formed from potassium hydroxide, sodamide, phenyllithium, and ethyl Grignard with desyl chloride. In each case carbazole was recovered.

In a flask equipped with condenser with drying tube were placed 4.15 g. of the potassium salt of carbazole, 4.59 g. of 1,2-diphenyl-1-methoxy-1,2-epoxyethane (V),⁷ and 80 ml. of dry dimethylformamide. The solution was heated under reflux 15 hr. After cooling the mixture was poured into ice water and the resulting mixture was extracted with chloroform. The chloroform solution was washed with water, dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was adsorbed on a neutral alumina column and eluted with hexane-chloroform (4:1). A yellow oil was first eluted, followed by *N*-desylcarbazole, and then carbazole. The *N*-desylcarbazole was recrystallized twice from aqueous acetic acid forming pale yellow plates, m.p. 179–182°. The yield was 1.52 g. (21% of the theoretical). This synthetic material gave no depression in melting point when mixed with the *N*-desylcarbazole obtained from I. The ultraviolet and infrared spectra of the two samples were identical.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Compounds Related to 22-Ketocholesterol

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22-Ketocholesterol² (I) and one form of 3 β -chloro-22-keto-5-cholestene (III) were prepared by alkylation with diisoamylcadmium of acid chlorides prepared from 3 β -acetoxy-5-bisnorcholelic acid. These steroids were converted, respectively, into 6 β -methoxy-3,5-cyclocholestan-22-one (methyl 22-keto-*i*-cholesteryl ether) (VIII) and 3,5-cyclocholesta-6,22-dione (*i*-cholesta-6,22-dione) (VI). Preparation of 3 β -chloro-22-keto-5-cholestene (III) by chlorination of 22-ketocholesterol (I) or by rearrangement of 6 β -methoxy-3,5-cyclocholestan-22-one (VIII) gave two similar isomeric products isolable because of different adsorptions on alumina. Attempted reduction of 6 β -methoxy-3,5-cyclocholestan-22-one (VIII) by Wolff-Kishner procedure appeared to fail.

This study of the properties of compounds prepared from 22-ketocholesterol (I) was part of a plan to prepare side-chain labeled cholesterol. 22-Ketocholesterol (I)² was prepared by hydrolysis of the keto ester furnished by the reaction of 3 β -acetoxy-5-bisnorcholelic chloride with diisoamylcadmium. The 3 β -chloro-22-keto-5-cholestene (III) (form B) was prepared most satisfactorily by the

action of diisoamylcadmium on crude 3 β -chloro-5-bisnorcholelic chloride. Chloroketone III prepared this way contained a single isomer and was more satisfactory than chloroketone produced either from 22-ketocholesterol (I) or 6 β -methoxy-3,5-cyclocholestan-22-one (VIII).

The 3 β -chloro-22-keto-5-cholestene (III) prepared by action of thionyl chloride on 22-ketocholesterol (I) or from 6 β -methoxy-3,5-cyclocholestan-22-one (VIII) was shown to exist as two very similar isomers. These were probably the two epimers that can exist at C-20. These isomers were separated by chromatography on alumina: A,

(1) Part of this work was abstracted from the Master of Science thesis of Z. F. Chmielewicz submitted to the faculty of De Paul University, 1952.

(2) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, 67, 1369 (1945).