Chemistry of Guareschi Imides I

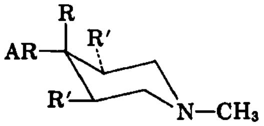
Lithium Aluminum Hydride Reduction of Some Bicyclo Guareschi Imides

By ARNOLD A. LIEBMAN† and FRANK E. DiGANGI

In the course of the synthesis of some 3,5-disubstituted piperidine compounds which would also contain the essential requirements for analgesic activity, some Guareschi imides were prepared and their subsequent reduction with lithium aluminum hydride was studied.

In an effort to prepare compounds of types I, II, and III as potential analgesics, Guareschi imides (IV) were synthesized as model compound intermediates. If lithium aluminum hydride would selectively reduce the imide grouping, then the intermediate dicyanopiperidines (V) could be converted into the desired compounds (I, II) and total reduction of these imides should yield III. A review of the literature shows no attempted selective reduction of cyanoimides. Avison and Morrison (1) have successfully reduced ethyl-5-chloro-2-cyano-2-phenylvalerate (VI) to 5-chloro-2-cyano-2-phenyl-1-pentanol (VII) but the lactam (VIII) derived from VII yielded only a mixture of basic products when selective reduction was attempted.

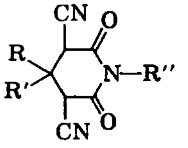
The model β,β-dialkyldicyanoimides (IV) were prepared using the modified procedure of Benica and Wilson (2) for the Guareschi reaction (3). It was noted that the Guareschi imides are insoluble in diethyl ether and other solvents commonly used in lithium aluminum hydride reductions, being only slightly soluble in tetrahydrofuran. Therefore, this solvent was used exclusively in the reduction studies. Selective reduction of the Guareschi imides was attempted under various conditions. Dissolving the imide in the minimum amount of peroxide-free tetrahydrofuran and adding a calculated amount of lithium aluminum hydride dissolved in tetrahydrofuran resulted in an immediate precipitate. For example, treating α,α′-dicyano-β,β-dimethyl-N-methylglutarimide (IX) with a molecular equivalent of lithium aluminum hydride resulted in the formation of a precipitate. The mixture was not heated but decomposed by adding water until refluxing had ceased. The solid material obtained by filtering the mixture was dissolved in hydrochloric acid and after extraction with ether, the solution alkalinized with sodium carbonate. After filtering the



I AR—C_6H_5 R—alkyl
R′—CH_3CH_2OOC—

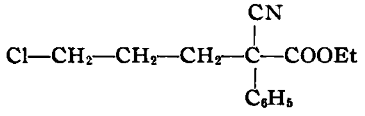
II AR—C_6H_5 R—alkyl
R′—CH_3CH_2CO—

III AR—C_6H_5 R—alkyl
R′—H_2NCH_2—



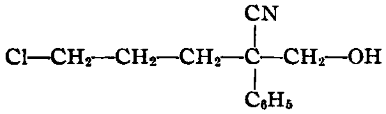
IV

R,R′—alkyl
R″—H, CH_3



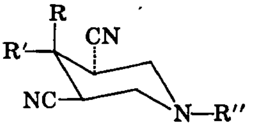
$$Cl—CH_2—CH_2—CH_2—\overset{\overset{\displaystyle CN}{|}}{\underset{\underset{\displaystyle C_6H_5}{|}}{C}}—COOEt$$

VI



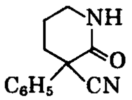
$$Cl—CH_2—CH_2—CH_2—\overset{\overset{\displaystyle CN}{|}}{\underset{\underset{\displaystyle C_6H_5}{|}}{C}}—CH_2—OH$$

VII

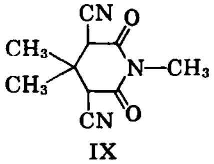


V

R,R′—alkyl
R″—H, CH_3



VIII



IX

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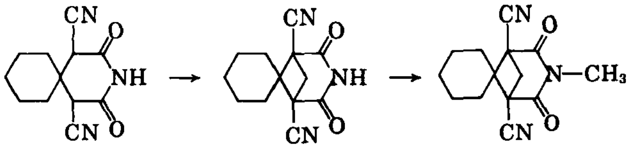
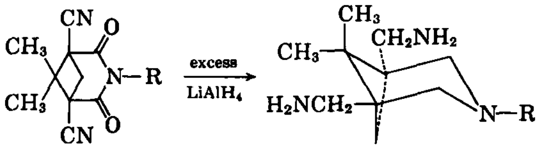


X XI XII



XIII R—H
XV R—CH₃

XIV R—H
XVI R—CH₃

resulting suspension followed by extraction with ether, evaporation of the ether left a small amount of solid material. This material melted higher than starting material and an infrared spectrum showed the retention of carbonyl and cyano functions. The organic solution from the reaction mixture deposited only starting material when evaporated. The original aqueous layer was evaporated to a small amount of impure semisolid, the quality of which precluded any attempts at characterization.

In addition, selective reduction was attempted allowing the reaction mixture to reflux for periods of from 2–24 hours and the complex being decomposed with either acid or alkali, extracting the organic material with suitable solvents. Also, increasing amounts of lithium aluminum hydride were used. In each instance, however, evaporation of the solvent left a small amount of hygroscopic semisolid but no pure reduction product could be isolated. Regardless of the compound or the experimental conditions, similar results were encountered.

It became apparent that the lithium aluminum hydride easily complexed with the acidic hydrogen atoms of the Guareschi imides and the resulting tetrahydrofuran insoluble material does not undergo the desired reduction. The preparation of XII[1] represents a compound having no acidic hydrogen. This compound was prepared by first synthesizing the Guareschi imide (X) from cyclohexanone, ethylcyanoacetate, and alcoholic ammonia. The bicyclo compound (XI) was prepared by the method of Kerr (4) and Paul (5), using sodium methoxide and methylene iodide. Methylation of the imide nitrogen was effected with sodium hydride and methyl iodide. Attempted selective reduction of this compound (XII) proceeded in a manner similar to the monocyclic compounds and gave similar results in that no pure reduction product could be identified.

Total reduction of the β,β-dialkyldicyanoglutarimides was attempted by adding a solution of the imide in tetrahydrofuran to an excess of lithium aluminum hydride contained in an ether-tetrahydrofuran mixture. Again, a precipitate formed, and regardless of the conditions used, no appreciable amounts of reduced material could be obtained.

Total reduction of a bicyclo Guareschi imide was attempted under the same conditions with the expected diaminomethylpiperidine being obtained. The Guareschi imide derived from acetone was converted into a bicyclo compound (XIII) with methylene iodide and subsequent reduction yielded 20% of the expected product (XIV). The N-methyl analog (XV) yielded 38% of the diaminomethyl-N-methylpiperidine (XVI) upon reduction.

Two unsymmetrical Guareschi imides were prepared to determine their susceptibility toward bicyclization with methylene iodide and subsequent reduction with lithium aluminum hydride. The Guareschi imide derived from 2-butanone was readily prepared. Due to the extremely low yield of Guareschi imide derived from 4-ı ethyl-2-pentanone in the Guareschi synthesis (6), this compound was prepared in an overall yield of 54% using the two step procedure for the preparation of β-alkyl-β-aryl Guareschi-like imides (7–9). These two Guareschi imides along with the two previously mentioned readily underwent bicyclization with methylene iodide yielding the products shown in Table I, Nos. 1–4. The sodio derivatives of the various bicyclo Guareschi imides were prepared with sodium hydride in tetrahydrofuran and each underwent N-methylation with methyl iodide (Table I, Nos. 5–8).

The general procedure for reduction of the bicyclo imides was patterned after the successful

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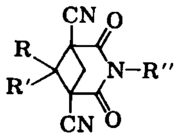
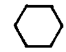
[1] Named according to the Ring Index, compound XII is: spiro-(3-aza-1,5-dicyano-2,4-dioxo-3-methyl-bicyclo-(3.1.1)-heptane-6,1′-cyclohexane).

TABLE I.—DATA FOR PREPARED COMPOUNDS



No.	R	R′	R″	Formula	M.p.,[a] °C.	Recrystallizing Solvent	Yield, %	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found
1	CH_3	CH_3	H	$C_{10}H_9N_3O_2$	319[c]	Methanol-acetone	46	. . .	. . .	. . .	. . .
2	CH_3	CH_2CH_3	H	$C_{11}H_{11}N_3O_2$	242–244	Ethanol	56	60.82	61.00	5.11	5.18
3	CH_3	$(CH_3)_2CHCH_2$	H	$C_{13}H_{15}N_3O_2$	243–245	Ethanol	66	63.66	63.66	6.16	6.13
4			H	$C_{13}H_{13}N_3O_2$	257–264[d]	Methanol	66	. . .	. . .	. . .	. . .
5	CH_3	CH_3	CH_3	$C_{11}H_{11}N_3O_2$	229–231	Absolute ethanol	85	60.82	60.67	5.11	5.16
6	CH_3	CH_2CH_3	CH_3	$C_{12}H_{13}N_3O_2$	174	Ethanol	55	62.32	62.48	5.66	5.74
7	CH_3	$(CH_3)_2CHCH_2$	CH_3	$C_{14}H_{17}N_3O_2$	204–208	Ethanol	98	64.85	65.29	6.61	6.78
8			CH_3	$C_{14}H_{15}N_3O_2$	247–249	Ethanol	87	65.35	65.53	5.88	6.00

[a] Melting points are uncorrected and were taken with a Thomas Hoover capillary tube melting point apparatus. [b] Analyses were performed by the Microanalytical Laboratory of the University of Minnesota. [c] Melts with decomposition. Reported (4) m.p., 305–306° (decompn.). [d] Reported (5) m.p., 266°.

reduction of 3-aza-1,5-dicyano-2,4-dioxo-6,6-dimethyl-bicyclo-(3.1.1)-heptane and its N-methyl analog (Nos. 1 and 5, Table I). It was found that a 30% excess of lithium aluminum hydride over the theoretical amount and a reflux time of 9 hours gave the best yields (Table II). The N-methyl-bicyclo-glutarimides gave slightly higher yields on reduction than those possessing the somewhat acidic free imide. The resulting compounds were extremely hygroscopic as were derivatives prepared from them. The purity of these compounds was established by elemental analysis of the base or of its picrate derivative and gas chromatograms. Compounds 11 and 15 (Table II) analyzed for tripicrate derivatives while compound 14 (Table II) appears to have formed a mixture of di- and tripicrate derivatives.

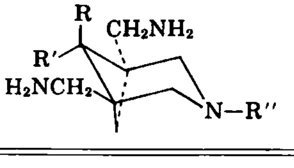
EXPERIMENTAL

General procedure for preparation of Guareschi Imides (2).—The appropriate ketone (0.5 mole), 1.1 mole of freshly distilled ethyl cyanoacetate, and 225 ml. of alcoholic ammonia were mixed and refrigerated for 3 days in a well-stoppered flask. The precipitated ammonium salt was collected and, after washing with ether, dissolved in approximately 350 ml. of warm water. Sufficient concentrated hydrochloric acid was added to insure complete precipitation and the imide then recrystallized from dilute alcohol.

The ketones used in this procedure were acetone, 2-butanone, and cyclohexanone.

Ethyl - (1 - isobutylethylidene) - cyanoacetate.—A mixture of 79.1 Gm. (0.07 mole) of ethyl cyanoacetate, 70.0 Gm. (0.7 mole) of 4-methyl-2-pentanone, 33.6 Gm. (0.56 mole) of glacial acetic acid, 10.8 Gm. (0.14 mole) of ammonium acetate, and 140 ml. of anhydrous benzene were placed in a flask fitted with a Dean-Stark water separator and

TABLE II.—DATA FOR PREPARED COMPOUNDS



No.	R	R′	R″	Formula	B.p. or m.p.,[a] °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
9	CH_3	CH_3	H	$C_{10}H_{21}N_3$	109–110/0.16 mm.	20	65.52	65.25	11.55	11.61
10	CH_3	CH_2CH_3	H	$C_{11}H_{23}N_3$	128–130/0.8 mm.	16	. . .	. . .	. . .	. . .
		tripicrate		$C_{29}H_{32}N_{12}O_{21}$	245–248[b]		39.37	39.63	3.65	3.77
11	CH_3	$(CH_3)_2CHCH_2$	H	$C_{13}H_{27}N_3$	136/0.3 mm.	10	69.28	69.02	12.08	11.90
12			H	$C_{13}H_{25}N_3$	155/0.45 mm.	23	69.90	69.92	11.28	11.30
13	CH_3	CH_3	CH_3	$C_{11}H_{23}N_3$	94–95/0.15 mm.	38	66.96	67.01	11.75	11.66
14	CH_3	CH_2CH_3	CH_3	$C_{12}H_{25}N_3$	115/0.4 mm.	29	68.19	69.34	11.92	11.84
		dipicrate		$C_{24}H_{32}N_9O_{14}$	209–210[b]		43.05	41.31	4.67	4.72
		tripicrate		$C_{30}H_{34}N_{12}O_{21}$			40.09	"	3.81	"
15	CH_3	$(CH_3)_2CHCH_2$	CH_3	$C_{14}H_{29}N_3$	125–127/0.5 mm.	47	70.23	68.60	12.21	12.15
		tripicrate		$C_{32}H_{38}N_{12}O_{21}$	205–207[b]		41.47	41.42	4.13	4.41
16			CH_3	$C_{14}H_{27}N_3$	138–140/0.5 mm.	21	70.83	70.48	11.46	11.74

[a] All reported boiling points are uncorrected. [b] Melts with decomposition.

treated according to the procedure of Cope (7). Distillation yielded 101.6 Gm. (72%) of the product boiling between 90–95°/0.6 mm.

α,α' - Dicyano - β - isobutyl - β - methylglutarimide.—According to the procedure of McElvain and Clemens (8, 9), 0.5 mole of sodium cyanoacetamide was treated with 0.5 mole of ethyl-(1-isobutylethylidene)-cyanoacetate. The product was dried to a constant weight of 87.3 Gm. (75%) and melted at 237–239°. Reported (6) m.p. 239–240°.

Selective Reduction Studies.—In a 1-L., three necked, round-bottom flask fitted with a stirrer, dropping funnel, condenser, and drying tube was placed a solution of 10.3 Gm. (0.05 mole) of α,α'-dicyano-β,β-dimethyl-N-methylglutarimide dissolved in 100 ml. of absolute tetrahydrofuran. The flask was cooled in an ice bath and a solution of 1.9 Gm. (0.05 mole) of lithium aluminum hydride dissolved in tetrahydrofuran[2] was added with stirring over a period of 1 hour. A solid began to separate after approximately one-half of the hydride solution was added. After the addition was completed, stirring was continued for 15 minutes at room temperature and then 100 ml. of water was cautiously added. The solid material was filtered with suction and washed with water. Five hundred milliliters of ether was added to the filtrate and the two layers separated. Evaporation of the aqueous layer under reduced pressure yielded a small amount of highly colored semisolid which could not be purified. The organic layer, when evaporated, left starting material only.

The solid obtained during the decomposition of the reaction mixture was dissolved in an excess of 6 *N* hydrochloric acid and the resulting solution extracted with ether. Upon evaporation of the ether, an additional small amount of starting material was obtained. The acidic solution was neutralized with sodium bicarbonate and the precipitated aluminum compounds filtered with suction. The filter cake was washed with ether and these washings were then used to extract the now alkaline solution. After drying the ethereal extract with anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, leaving approximately 0.5 Gm. of a white solid. This material was recrystallized several times from 50% ethanol and melted at 206°. The infrared spectrum of this compound showed retention of carbonyl and nitrile functions.

Selective reduction was also attempted under the experimental conditions of increasing reflux periods up to 24 hours and/or decomposing the hydride complex with 10% sulfuric acid (10). In addition, increasing amounts of lithium aluminum hydride, up to 100% excess, were used. In each instance, the apparent reduction product(s) consisted of highly colored, ether-insoluble semisolid material. Typical amine salts such as methiodide, hydrochloride, citrate, etc., were prepared from tetrahydrofuran solution, but were of such a hygroscopic nature that purification could not be effected. Attempts to purify the reduced material by microdistillation *in vacuo* were unsuccessful in that the material resinified.

The imides used in these studies were α,α'-dicyano-β,β-dimethylglutarimide, α,α'-dicyano-β,β-dimethyl-N-methylglutarimide, and spiro-(3-aza-1,5-dicyano-2,4-dioxo-3-methyl-bicyclo-(3.1.1)-heptane-6,1′-cyclohexane).

Total Reduction Studies.—A suspension of 15.5 Gm. of 95% lithium aluminum hydride (0.39 mole) in a mixture of 150 ml. of absolute ether and 50 ml. of absolute tetrahydrofuran was heated under reflux for 1 hour to effect solution of the hydride. After cooling, 15.3 Gm. (0.08 mole) of α,α'-dicyano-β,β-dimethylglutarimide dissolved in 350 ml. of absolute tetrahydrofuran was added dropwise with stirring. When the addition was completed, the reaction mixture was stirred and heated under reflux for 7 hours during which time a thick, dark yellow precipitate appeared. The mixture was cooled and decomposed by cautiously adding 16 ml. of water, 16 ml. of 15% sodium hydroxide solution, and 48 ml. of water. The gelatinous precipitated material was removed by filtration and washed with two 50-ml. portions of tetrahydrofuran. The combined filtrates, which had a yellow color, were dried (anhydrous sodium sulfate) and then evaporated under reduced pressure. The residue consisted of 3.6 Gm. of starting material and approximately 100 mg. of a dark yellow oil having amine characteristics. A stable solid derivative could not be prepared from this oil.

This reduction was also attempted using 50% excess lithium aluminum hydride in addition to the theoretical amount required to reduce the imide and two nitrile groups. The reflux time was increased to 24 hours but no change in the results was noted. Similar results were obtained in the attempted total reduction of α,α'-dicyano-β,β-dimethyl-N-methylglutarimide.

3-Aza-1,5-dicyano-6,6-dimethyl-2,4-dioxo-bicyclo-(3.1.1)-heptane.[3]—Following the procedure of Kerr (4) and Paul (5), 61.2 Gm. (0.32 mole) of α,α'-dicyano-β,β-dimethylglutarimide was converted into its trisodium salt and treated with 129.0 Gm. (0.048 mole) of methylene iodide. The crude product recovered from aqueous acid weighed 30.0 Gm. (46%) and melted between 305–315° (decompn.). When recrystallized from methanol and acetone, the melting point was raised to 319° (decompn.). Reported (4) m.p. of the product recrystallized from glacial acetic acid is 305–306° (decompn.).

3-Aza-1,5-dicyano-2,4-dioxo-3,6,6-trimethyl-bicyclo-(3.1.1)-heptane.—Sodium hydride, 6.6 Gm. of a 54.5% dispersion (0.15 mole), was suspended in 100 ml. of absolute tetrahydrofuran contained in a 1-L., three-necked, round-bottom flask equipped with a stirrer, dropping funnel, reflux condenser, and drying tube. To the suspension, 30.0 Gm. (0.15 mole) of 3-aza-1,5-dicyano-6,6-dimethyl-2,4-dioxo-bicyclo-(3.1.1)-heptane dissolved in 300 ml. of absolute tetrahydrofuran was added dropwise with stirring. The reaction mixture was refluxed for 1 hour, cooled, and 24.0 Gm. (0.17 mole) of methyl iodide added. Stirring and reflux were continued for $2^1/_2$ hours and after cooling, 20 ml. of water was added. The solution was evaporated under reduced pressure leaving 28.8 Gm. (85%) of the crude product melting at 222–226°. The product was recrystallized from ethanol and melted at 229–231°.

3-Aza-1,5-diaminomethyl-6,6-dimethyl-bicyclo-(3.1.1)-heptane.—Lithium aluminum hydride, 8.4

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[2] Prepared according to directions given by Rapoport and Payne (10).

[3] This and the following procedures are typical of those used for the preparation of compounds listed in Tables I and II.

Gm. of 95% purity (0.21 mole), was crushed and suspended in a mixture of 150 ml. of absolute ether and 50 ml. of absolute tetrahydrofuran contained in a 2-L., three-necked, round-bottom flask fitted with a dropping funnel, stirrer, condenser, and drying tube. The suspension was heated under reflux for 1 hour, cooled and 10.2 Gm. (0.05 mole) of 3-aza-1,5-dicyano-6,6-dimethyl-2,4-dioxo-bicyclo-(3.1.1)-heptane dissolved in 350 ml. of absolute tetrahydrofuran was added with stirring. After the addition was completed, stirring and reflux were continued for 9 hours. The reaction mixture was cooled and the complex decomposed by the cautious addition of 9 ml. of water, 9 ml. of 15% sodium hydroxide solution, and 27 ml. of water. The granular precipitate that had formed was filtered and washed with ether, the washings being added to the previous filtrate which was then dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue of 3.4 Gm. distilled. The fraction boiling between 109–110°/0.16 mm. was collected and weighed 1.8 Gm. (20%).

The distilled material solidified at room temperature and attempts to prepare solid derivatives from it resulted in hygroscopic compounds which could not be purified.

3-Aza-1,5-diaminomethyl-6-ethyl-6-methyl-bicyclo-(3.1.1)-heptane Tripicrate.—Reduction of the bicyclo Guareschi imide derived from 2-butanone yielded 16% of the product. However, the material was too hygroscopic to have analyzed. A picrate derivative was readily formed but decomposed into picric acid and the triamine when recrystallization from conventional solvents was attempted. A stable tripicrate was prepared by dissolving 0.5 Gm. of the triamine in 1 ml. of absolute ethanol and slowly adding 22 ml. of a saturated solution of picric acid in absolute ethanol. The precipitated derivative was collected and purified by washing it with chloroform and decanting the solvent. This process was repeated six times using ethanol as the washing medium and finally the solid derivative was dried in a vacuum, m.p. 245–248° (decompn.).

SUMMARY

1. Five Guareschi imides were prepared by known procedures.

2. Selective reduction of the imide grouping of the Guareschi imides with lithium aluminum hydride uniformly resulted in ether-insoluble semisolids from which no pure product could be isolated or characterized.

3. Total reduction of the imide grouping and the nitrile groups of the Guareschi imides gave similarly poor results.

4. A series of four bicyclo Guareschi imides was prepared from the monocyclic Guareschi imides.

5. The four bicyclo Guareschi imides prepared readily underwent N-methylation.

6. Lithium aluminum hydride reduction of the four bicyclo Guareschi imides and their N-methyl analogs yielded the expected totally reduced products.

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ERRATUM

In the paper titled "Proposed Method of Assay for Diaphene" (1), the formula for calculating the per cent of Diaphene in paragraph three at page 45 should read:

$$\text{per cent Diaphene} = \frac{A \times 50 \times 100}{I \times V \times W} \times 100$$

(1) Soliman, S. A., and Harris, L. E., THIS JOURNAL, **52**, 43(1963).