

ALKYLATION OF CYCLIC 1, 3-DIKETONES WITH MANNICH BASES FROM INDOLES

BY S. SWAMINATHAN AND V. T. RAMAKRISHNAN

(Department of Organic Chemistry, University of Madras, Madras-25, India)

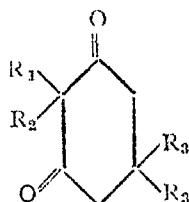
Received September 30, 1964

(Communicated by Dr. K. N. Menon, F.A.Sc.)

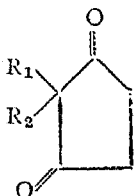
INTRODUCTION

GRAMINE and other related Mannich bases from indole have been made to react with a number of nucleophilic compounds to effect diverse types of alkylations.¹ These bases do not appear so far to have been used for alkylation of cyclic 1, 3-diones. The present study deals with such alkylations.

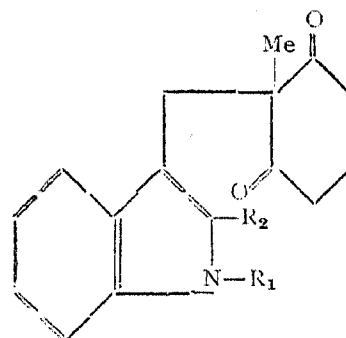
The diketones so alkylated include cyclohexane-1, 3-dione (I) 2-methyl-cyclohexane-1, 3-dione (II), 5, 5-dimethyl-cyclohexane-1, 3-dione (III) and 2-methyl-cyclopentane-1, 3-dione (IV). These alkylations took place smoothly, in general, in refluxing benzene, toluene or xylene *without* any added catalyst.



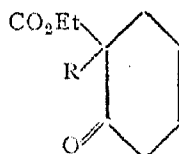
- I $R_1 = R_2 = R_3 = H$
 II $R_1 = Me, R_2 = R_3 = H$
 III $R_1 = R_2 = H, R_3 = Me$
 V $R_1 = R_2 = 3\text{'-indolylmethyl}, R_3 = H$
 VI $R_1 = R_2 = 3\text{'-indolylmethyl}, R_3 = Me$



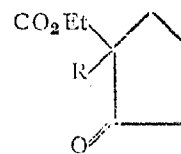
- IV $R_1 = Me, R_2 = H$
 IX $R_1 = Me, R_2 = 3\text{'-indolylmethyl}$



- VII $R_1 = R_2 = H$
 X $R_1 = Me, R_2 = H$
 XI $R_1 = H, R_2 = Me$



XII



XIII

- XII and XIII, R = 3'-indolylmethyl

The diones I and III furnished exclusively bis-alkylated products, *viz.*, 2, 2-bis-(3'-indolylmethyl)-cyclohexane-1, 3-dione (V) and 2, 2-bis-(3'-indolylmethyl) 5, 5-dimethyl-cyclohexane-1, 3-dione (VI) respectively in 76% and 55% yields even when equimolar amounts of reactants were employed. Apparently the monoalkylated products formed initially undergo alkylation more readily than the parent diones. The alkylation of II gave consistent yields (80-85%) of 2-(3'-indolylmethyl)-2-methyl-cyclohexane-1, 3-dione (VII). In this reaction with sodium hydroxide in toluene medium as condensing agent, a side product was isolated from the aqueous alkaline washings identified as 5-oxo-6-(3'-indolylmethyl)-heptanoic acid (VIII) also obtained directly from VII by refluxing with 4% sodium hydroxide solution. Such cleavages of cyclic-1, 3-diketones are well known.² The alkylation of IV with gramine without any added catalyst, furnished 2-(3'-indolylmethyl)-2-methyl-cyclopentane-1, 3-dione (IX) in 61% yield. For comparison, the alkylations of II with 1-methyl and 2-methylgramines were also carried out. As noted elsewhere³ 1-methylgramine was sluggish in its reaction and gave only 10% of the corresponding product X and even then required a catalyst. 2-Methylgramine was more reactive furnishing the alkylated product XI in 85% yield. There was no evidence of cyclization between one of the carbonyls and the methyl group in the indole portion, similar to that reported⁴ in the reaction of 2-methyl indole with 2-formylcyclohexanones.

In contrast to the smooth alkylations of the above diketones requiring no added catalyst, the alkylation of 2-carbethoxy cyclohexanone and 2-carbethoxy-cyclopentanone with gramine could be done only in the presence of sodium hydroxide pellets in refluxing xylene. The yields of the alkylated products XII and XIII were 91% and 57% respectively. The various alkylated products referred to above had their main U.V. absorptions at *Ca* 222 and 283 $m\mu$ characteristic of the indole ring. As for their I.R. absorptions, we have reported⁵ these elsewhere.

Compounds VII, IX and XII were treated with a variety of acidic catalysts with a view to effect ring closure between the carbonyl carbon and the 2-position of the indole nucleus. Such a cyclization seemed possible in the light of a number of reported⁶⁻⁸ electrophilic substitutions at the 2-position in skatole and its derivatives. The desired cyclizations could not however be realised as also the attempted cyclization of the diol obtained by lithium aluminium hydride reduction of VII.

TABLE
Alkylations with gramine

Sl. No.	Reactants (moles)	Solvent vcl. ml.	Time of reflux hrs.	Catalyst	Product or products	m.p. and crystallization solvents
1	Cyclohexane-1, 3-dione (I) ⁹ (0.04) and gramine (0.04)	Benzene 200	14	None	2, 2-Bis-(3'-indolylmethyl) Cyclohexane-1, 3-dione (V) ^b	197.5-198° Benzene
2 a	2-Methylcyclohexane-1, 3-dione (II) ¹⁰ (0.04) and gramine (0.04)	Benzene 70	30	None	2-methyl-2-(3'-indolylmethyl)-cyclohexane 1, 3-dione (VII)	168-69° Ethanol
2 b	do. (0.02 mole each)	Toluene 200	15	0.5 g. NaOH	VII ——— and 5-oxo-6-(3'-indolylmethyl)-heptanoic acid (VIII) ^c ———	do. 115-116° Benzene petroleum ether
3	5, 5-Dimethyl-cyclohexane-1, 3-dione (III) (0.015) and gramine (0.03)	Benzene 100	20	None	2, 2-Bis-(3'-indolylmethyl) 5, 5-dimethyl-cyclohexane-1, 3-dione (VI) ^d	162-63° Ethylacetate- petroleum ether
4	2-Methylcyclopentane-1, 3-dione ¹¹ (IV) (0.03) and gramine (0.03)	Benzene 160	30	None	2-methyl-2-(3'-indolylmethyl)-cyclopentane-1, 3-dione (IX)	129-30° Ethylacetate- petroleum ether
5	1-Methylgramine (0.017) and II (0.017)	Xylene 70	30	0.2 g. NaOH	2-methyl-2-(1'-methyl-3'-indolylmethyl) cyclohexane 1, 3-dione (X) ^{e, f}	92-93° Petroleum ether
6	2-Methylgramine (0.0053) and II (0.005)	Benzene 25	50	None	2-methyl-2-(2'-methyl-3'-indolylmethyl) cyclohexane-1, 3-dione (XI)	174-75° Benzene
7	2-Carboethoxy cyclohexanone (0.059) and gramine (0.057)	Xylene 200	12	0.5 g. NaOH	2-Carboethoxy-2-(3'-indolylethyl) cyclohexanone (XII) ^g	97-98° Benzene- petroleum ether
8	2-Carboethoxy-cyclopentanone (0.08) and gramine (0.08)	Xylene 200	12	0.5 g. NaOH	2-Carboethoxy-2-(3'-indolylmethyl) cyclopentanone (XIII) ^{h, i} and neutral product (XIV) ^j	76-77° Benzene- petroleum ether 188-89° Benzene

(a) The use of higher boiling solvents, toluene and xylene, decreased the yield.

(b) With 0.01 mole of I and 0.004 mole of gramine, under similar conditions, the same product V was obtained.

(c) Neutralisation equivalent: Found 270.4, Calculated 273.3.

(d) With 0.036 mole of III and 0.036 mole of gramine, under similar conditions, 55% yield of VI was obtained.

(e) Unreacted 1-methylgramine and the dione II were recovered from the acid and alkaline washings.

(f) The same experiment in the absence of the catalyst did not furnish X.

(g) None of this product was formed in the absence of the catalyst.

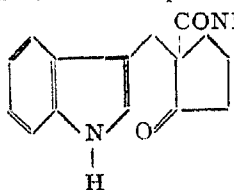
(h) The xylene layer, after washing with dilute hydrochloric acid, water, and sodium bicarbonate solution, was concentrated to give a semi-solid. Trituration with a mixture of ethylacetate and petroleum ether (40-60°) afforded XIV. The filtrate was stripped of solvent and the residue chromatographed in benzene solution over alumina to give crystalline XIII.

I

and substituted gramines

Yield %	Molecular formula of product	Found			Calculated			$\lambda_{\text{EtOM max.}}$ ($\log_{10} \epsilon$)
		C	H	N	C	H	N	
76	C ₂₄ H ₂₂ N ₂ O ₂	77.7	5.9	..	77.8	5.9	..	221 (4.77) 282 (4.10)
86	C ₁₆ H ₁₇ NO ₂	75.1	7.0	5.3	75.3	6.7	5.5	220 (4.55) 282 (3.91)
57
18	C ₁₆ H ₁₉ NO ₃	4.8	5.1	..
55	C ₂₆ H ₂₆ N ₂ O ₂	77.9	6.7	7.1	78.4	6.5	7.0	221 (4.83) 281 (4.12)
61	C ₁₅ H ₁₅ NO ₂	74.3	6.4	6.0	74.7	6.2	5.8	220 (4.5) 275 (3.95)
10	C ₁₇ H ₁₉ NO ₂	75.9	7.1	..	75.8	7.1	..	222 (4.45) 288 (3.58)
85	C ₁₇ H ₁₉ NO ₂	75.6	7.1	..	75.8	7.1	..	223 (4.58) 283 (3.98)
91	C ₁₈ H ₂₁ NO ₃	72.5	7.1	..	72.3	7.0	..	222 (4.54) 283 (3.84)
57	C ₁₇ H ₁₉ NO ₃	71.5	5.6	..	71.6	5.7	..	220 (4.54) 281 (3.81)
5	9.2	224 (4.56) 283 (3.82)

(i) The same reaction was carried out in refluxing benzene (48 hrs. with no added catalyst) and toluene (5 hrs. in the presence of NaOH) to give only slightly decreased yields of XIII. However, in the first case, none of the side product XIV could be isolated.

(j) This is believed to be  though no further work was done to prove

the structure.

(k) The m.p.'s given are those of analytical samples.

EXPERIMENTAL

Alkylations with Indole Mannich Bases

The various alkylations were in general carried out in nitrogen atmosphere by refluxing the reactants together in benzene, toluene or xylene medium with or without solid sodium hydroxide pellets. The procedures detailed below for the alkylation of 2-methylcyclohexane-1, 3-dione (II) with gramine are typical.

Procedure A.—A solution of gramine (7.0 g., 0.04 mole) and II (5.0 g., 0.04 mole) in dry benzene (70 ml.) was refluxed. Dimethylamine evolved steadily during this period. After 30 hours when the evolution of dimethylamine almost stopped, the reaction mixture was cooled. The crude product (8.6 g., m.p. 155–57°) separated and was collected. The filtrate was washed successively with water, dilute hydrochloric acid and again water and then concentrated to give an additional amount (0.4 g.) of product. The combined crops were crystallized from ethanol to give 8 g. of VII, m.p. 162–63°. After four crystallizations from the same solvent, the analytical sample had m.p. 168–69°.

Procedure B.—A mixture of gramine (3.5 g., 0.02 mole), II (2.5 g., 0.02 mole) and powdered sodium hydroxide (0.5 g.) in dry toluene (200 ml.) was refluxed for 15 hours. The reaction mixture was cooled when compound VII (2.0 g., m.p. 161–62°) separated and was collected, washed with water and dried. The alkaline washings when acidified gave the crude acid VIII (1.0 g.) which was repeatedly crystallized from a mixture of benzene and petroleum ether (60–80°) to give material, m.p. 115–16°. The toluene filtrate was washed with dilute hydrochloric acid and water and then concentrated to give a further 0.9 g. of VII.

The experimental details and other data for the alkylations carried out are summarised in Table I.

Cis-2-Methyl-trans-2-(3'-indolylmethyl)-cyclohexane-1, 3-cisdiol (XV)

To a suspension of lithium aluminium hydride (1.0 g.) in tetrahydrofuran (15 ml.) was added dropwise a solution of VII (3.0 g.) in tetrahydrofuran (50 ml.) with stirring. After an hour, the mixture was refluxed for 2 hours with continued stirring. The reaction mixture was cooled, treated with excess ethylacetate and the solvent removed *in vacuo*. The residue was acidified with cold dilute sulphuric acid and extracted with ethylacetate. The extract after washing with water and concentration furnished XV (1.8 g.),

m.p. 132–35°. The analytical sample was crystallized from benzene-petroleum ether (60–80°) and had m.p. 143–44°. Found: C, 74.2; H, 8.0; N, 5.7. $C_{16}H_{21}NO_2$ requires: C, 74.1; H, 8.1; N, 5.4%. $\lambda_{\max}^{CHCl_3}$ 2.7 μ (*m*) 2.82 μ (*s*) and no carbonyl absorption.

The configuration assigned for the above diol is based on the fact that hydride reductions usually lead predominantly to equatorial hydroxy compounds and the assumption that the 3-indolylmethyl substituent is probably bulkier than the methyl group and may be expected to have the more stable equatorial orientation.

Attempted Cyclization of XV

A solution of XV (0.5 g.) and *p*-toluene sulphonic acid (50 mg.) in dry benzene (50 ml.) was refluxed for 5 hours. The benzene solution was washed and then concentrated. The residue was dissolved in ethylacetate (5 ml.) and put on an alumina column. Two fractions were collected by successive elution with 25% and 50% benzene in petroleum ether (40–60°). The second fraction gave product (300 mg., m.p. and mixed m.p. 142–44°) with authentic XV. The first fraction gave product (50 mg.) which was recrystallized from benzene; m.p. 199–200°. Found: C, 74.5; H, 8.3. $C_{16}H_{21}NO_2$ requires: C, 74.1; H, 8.1%. λ_{\max}^{Nujol} 3.05 μ (*s*) and no carbonyl absorption. This product is believed to be an epimer of XV.

Compound XV was recovered unreacted by treatment at room or reflux temperature with phosphorous pentoxide in benzene.

5-Oxo-6-(3'-Indolylmethyl)-heptanoic Acid (VIII)

A mixture of VII (2.0 g.) and 4% sodium hydroxide solution (12 ml.) was refluxed for 3 hours. The mixture was cooled, diluted and extracted with ether. The aqueous layer was acidified with dilute hydrochloric acid when VIII (1.7 g.) crystallized out. A sample recrystallized from a mixture of benzene and petroleum ether (60–80°) had m.p. 115–16° undepressed by acidic side product obtained in the alkylation of II with gramine in the presence of solid sodium hydroxide. λ_{\max}^{KBr} 2.8 μ (*s*) and 5.79 μ (*s*).

SUMMARY

The alkylations of some cyclic 1, 3-diketones with gramine and substituted gramines and the alkylations of 2-carbethoxycyclohexanone and 2-carb-ethoxycyclopentanone with gramine are described.

ACKNOWLEDGEMENTS

The authors are indebted to Mr. R. Balasubramanian for carrying out some of the analyses, and also to Ricker Laboratories Inc., Northridge, California, for generous supplies of indole. One of the authors (V. T. R.) thanks the University of Madras for the award of a Research Assistantship.

REFERENCES

1. Brewster, J. and Eliel, E. L. *Org. Reactions*, 1953, 7, 99.
2. Stetter, H. .. *Angew. Chem.*, 1955, 67, 769.
3. Snyder, H. R. and Eliel, E. L. *J. Am. Chem. Soc.*, 1948, 70, 1073, 3855, 4233.
4. Noland, W. E. and Johnson, J. E. *Tetrahedron Letters*, 1962, 589.
5. Ramakrishnan, V. T., Shanmugam, P. and Swaminathan, S. *Ind. J. Chem.*, 1963, 1, 406.
6. Noland, W. E. and Robinson, D. N. *Tetrahedron*, 1958, 3, 68.
7. Treibs, A. and Herrmann, E. *Ann.*, 1954, 589, 207.
8. Plieninger, H. and Suehiro, T. *Ber.*, 1955, 88, 550.
9. Thompson, R. B. .. *Org. Syn.*, 1958, Coll. 3, 278.
10. Mckler, A. B., Ramachandran, S., Swaminathan, S. and Newman, M. S. *Ibid.*, 1961, 41, 56.
11. Swaminathan, S., John, J. P., Venkataramani, P. S. and Viswanathan, K. *Proc. Ind. Acad. Sci.*, 1963, 57 A, 44.