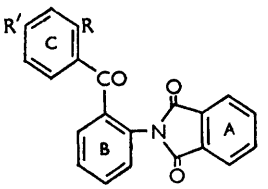
540. *Triazepines. Part I.* 1,2,4-*Triazacyclohepta*-2,5,7-*trienes.*

By (Miss) E. J. Engels, M. Lamchen, and A. J. Wicken.

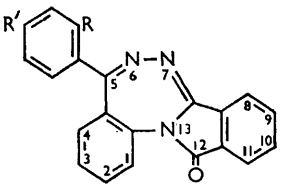
2,4-Dimethoxy- (Ia) and 4-methoxy-2′-phthalimidobenzophenone (Ib) with hydrazine in boiling alcohol give products whose chemical and spectral properties indicate that they are 1,2,4-triazacyclohepta-2,5,7-trienes (II). In contrast, with this, 4-methoxy-2′-phthalimidodiphenylmethane is decomposed by hydrazine according to the Ing and Manske reaction. 2-Phthalimidobenzophenone, β-phthalimidopropiophenone, and 2,4-dimethoxy-β-phthalimidopropiophenone also undergo the normal Ing and Manske decomposition by hydrazine.

Only a few triazacycloheptatrienes (triazepines) have been reported, mainly as di-, tetra-, or hexa-hydro- or benzo-derivatives. The 1,3,5-triaza-system has received most attention; 1,2,5-, 1,3,6-, and 2,3,4-triaza-systems have also been reported, but not investigated. Before our short communication [1] no 1,2,4-triazacycloheptatriene had been reported, though reduced derivatives had been referred to in three instances,[2] but not fully investigated.

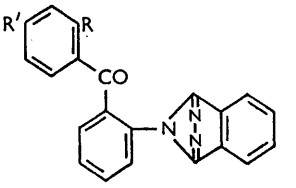
The tosyl group proving difficult to remove in our experiments, we used the phthaloyl group to protect the amino-group of anthranilic acid during a Friedel–Crafts condensation with dimethylresorcinol. 2,4-Dimethoxy-2′-phthalimidobenzophenone (Ia) was then obtained readily and in good yield. When we attempted to remove the phthaloyl group by refluxing an alcoholic suspension of the phthalimide (Ia) with hydrazine,[3] the phthalimide slowly dissolved whilst white needles (A) crystallised. Analysis showed that the



(Ia): R = R′ = OMe
(Ib): R = H, R′ = OMe
(Ic): R = R′ = H



(IIa): R = R′ = OMe
(IIb): R = H, R′ = OMe



(III)

product contained both the nitrogen atoms of the hydrazine, and we suggested [1] that the product formed had structure (IIa).

A structure such as (III; R = R′ = OMe) is unlikely on the basis of known stable bond angles and since its formation should not be affected by groups on ring c (see I) as has been shown to be the case.[1]

Compound A could not be acetylated, contained no active hydrogen, and was stable to refluxing 10N-hydrochloric acid or 5N-sodium hydroxide. These results eliminate a monohydrazone grouping $=N\cdot NH_2$. The molecular weight (microebullioscopic in chloroform [4]) was 368, in good agreement with the structure (IIa).

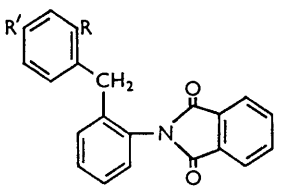
Replacement of the benzophenone-carbonyl group by a methylene group should prevent condensation with hydrazine to a product of type (II). Since it was found that *o*-phthalimidobenzoic acid was readily reduced to *N*-*o*-carboxyphenylphthalimidine by Clemmensen's method, 2,4-dimethoxy-2′-phthalimidodiphenylmethane (IVa) could

[1] Engels, Lamchen, and Wicken, *Proc. Chem. Soc.*, 1958, 191.
[2] Tingle and Bates, *Amer. Chem. J.*, 1914, **36**, 260; Busch, *Ber.*, 1894, **27**, 2901; Losse and Uhlig, *Chem. Ber.*, 1957, **90**, 257.
[3] Ing and Manske, *J.*, 1926, 2348.
[4] Sucharda and Bobranski, " Elementary Analysis of Organic Compounds," Gallenkamp and Co. Ltd., London, 1936, p. 34.

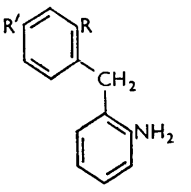
not be prepared directly from the corresponding benzophenone, so we attempted to prepare 2-amino-2′,4′-dimethoxydiphenylmethane (Va).

However, the intermediate 2-amino-2′,4′-dimethoxybenzophenone (VIa) could be obtained only in very small yield. Friedel–Crafts reaction of dimethylresorcinol and the chloride of *N*-toluene-*p*-sulphonylanthranilic acid gave the expected benzophenone, but hydrolysis of the amide group gave only small yields of the amino-compound (VIa) mixed with sulphonated products. Hofmann degradation of 2-(2,4-dimethoxybenzoyl)benzamide was unsuccessful. Similarly 2-(2,4-dimethoxybenzyl)benzoic acid, prepared as described by Tambor,[5] was converted into the amide but could not be degraded to the amine (Va) by the Hofmann degradation (hypobromite or hypochlorite), the Schmidt reaction, or the Curtius reaction.

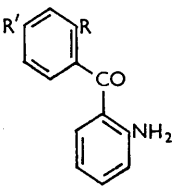
Then, 4-methoxy-2′-phthalimidobenzophenone (Ib), obtained from a Friedel–Crafts reaction of *o*-phthalimidobenzoyl chloride with anisole, on treatment with hydrazine gave a condensation product which, as it was analogous to compound (A), we considered to have structure (IIb). So attempts were made to prepare 4-methoxy-2′-phthalimidodiphenyl-



(IVa): R = R′ = OMe
(IVb): R = H, R′ = OMe



(Va): R = R′ = OMe
(Vb): R = H, R′ = OMe



(VIa): R = R′ = OMe
(VIb): R = H, R′ = OMe

methane (IVb). 2-Amino-4′-methoxybenzophenone (VIb) was readily obtained by the method of Simpson *et al.*;[6] its reduction was however dependent on the method used. Zinc dust in alkali, Clemmensen reduction, Wolff–Kishner reduction, and the Huang-Minlon[7] modification thereof, failed to give the expected product. Catalytic hydrogenation with palladium–charcoal failed, but with Adams catalyst one mol. of hydrogen was absorbed. This suggested reduction to the alcohol only, and although this oily product was not obtained pure it formed a picrate which gave correct analyses for the alcohol. This was surprising since Hartung and Crossley[8] found that palladium–charcoal was effective for reduction of propiophenones, and that no hydrogenation took place with platinised charcoal; they further found that this hydrogenation did not appear to proceed via the alcohol. The method of Hewett *et al.*[9] of reducing *o*-aminobenzophenone with sodium in ethanol was found to give good yields of the diphenylmethane (Vb); fusion of this with phthalic anhydride gave the phthalimide (IVb).

Refluxing a suspension of the imide (IVb) in ethanol with hydrazine produced phthalhydrazide and the free amine (Vb), and no condensation product, as expected.

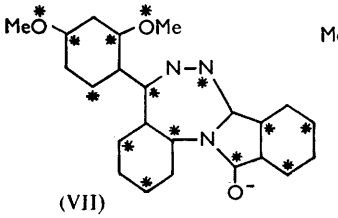
Models (" Catalin ") showed that the suggested structure (II) would, with some slight strain, fit the normal valency angles. The triazepine ring is however buckled, and the phenyl group B (see II) projects at an angle from a planar ring-system. Structure (II), however, has many canonical forms (VII, where * indicates possible positions of the positive charge); some of which produce completely planar structures, *e.g.*, (VIII) and (IX); (VIII), with complete aromaticity, is probably the most important. The high degree of resonance also accounts for the great stability of the compound.

Models further indicated that 3- and 4-phthalimidobenzophenones could not form

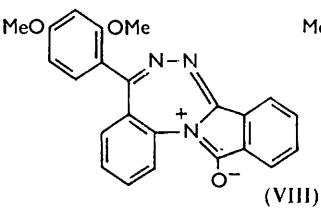
[5] Tambor, *Ber.*, 1910, **43**, 1886.
[6] Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 646.
[7] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[8] Hartung and Crossley, *ibid.*, 1934, **56**, 158.
[9] Hewett, Lermit, Openshaw, Todd, Williams, and Woodward, *J.*, 1948, 292.

similar condensation products since the =N–N= group could not bridge the benzophenone- and the phthalimido-carbonyl group. 2,4-Dimethoxy-3′- and -4′-phthalimidobenzophenone were prepared by Friedel–Crafts reactions from *m*- and *p*-phthalimidobenzoyl chloride respectively with dimethylresorcinol, and on treatment with hydrazine both gave the normal Ing and Manske decomposition.

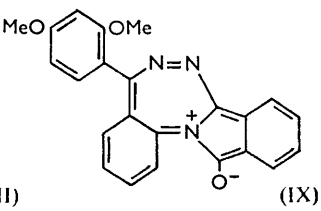
A structure such as (VIII) should confer colour on the compound. Our products are colourless; but although there is practically no absorption down to 400 mμ, there is a



(VII)



(VIII)



(IX)

rapid rise in ε just outside the visible region, and at 380 mμ log ε exceeds 4, and it retains this value to the limit of our determination (225 mμ). A few broad peaks and one sharp peak are found above this general plateau. The positions of the absorption bands, both ultraviolet and infrared, of compounds considered as (IIa and b) are almost identical, confirming the similarity of structure.

Infrared spectra of compounds were consistent with the suggested structures (IIa and b) and excluded all alternatives. No benzophenone-carbonyl absorption and no N–H stretching vibration of a primary or secondary amino-group is present. A phthalimido-group should show two absorption bands, arising from the two carbonyl groups; the compounds (IIa and b) have only one absorption band (at 1712 cm.$^{-1}$) corresponding to a single αβ-unsaturated carbonyl group located in a five-membered ring (1716 cm.$^{-1}$).[10]

When 2-phthalimidobenzophenone (Ic), prepared by fusion of 2-aminobenzophenone with phthalic anhydride, was similarly treated with hydrazine no triazepine was formed; instead, the normal Ing and Manske decomposition give almost quantitative yields of 2-aminobenzophenone and phthalhydrazide. The substituents on ring c thus influence the course of the reaction.

To obtain information about the mechanism and the scope of the condensation, other phthalimidophenones with the grouping ·CO·C·C·N·CO· were prepared. β-Phthalimidopropiophenone, and 2,4-dimethoxy-β-phthalimidopropiophenone were prepared by Friedel–Crafts condensation of 3-phthalimidopropionyl chloride with benzene and dimethylresorcinol respectively. With hydrazine in boiling alcohol these underwent the normal decomposition to phthalhydrazide, and no condensation product could be isolated from 2-benzamido-5-methylbenzophenone.

The initial reaction of hydrazine with β-phthalimidopropiophenone and 2,4-dimethoxy-β-phthalimidopropiophenone must have been on a phthalimido-carbonyl group as phthalhydrazide was produced in both cases. It can thus be assumed that since 2-phthalimidobenzophenone also produced phthalhydrazide the initial attack here and thus on 2,4-dimethoxy-2′-phthalimidobenzophenone, which produced the triazepine, was also on a carbonyl group of the phthalimido-residue. Electron-repelling *ortho*- and/or *para*-groups in ring c could activate the benzophenone-carbonyl group sufficiently to make it react with the NH_2-group of the hydrazide formed provided other factors are favourable, and provided the initial attack is an electrophilic attack on the oxygen atom. Activation, in this sense, of the carbonyl group alone is not sufficient to effect triazepine formation since

[10] Bellamy, " The Infra-Red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 2nd edn., 1958, p. 149; Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 956; Fuson, Josien, and Shelton, *ibid.*, 1954, **76**, 2526.

2,4-dimethoxy-β-phthalimidopropiophenone gave the normal Ing and Manske decomposition.

Stereochemical effects may be operative since the substitution of a $\cdot CH_2 \cdot CH_2 \cdot$ chain, as in 2,4-dimethoxy-β-phthalimidopropiophenone, for an *ortho*-phenylene group in 2,4-dimethoxy-2′-phthalimidobenzophenone (Ia) caused decomposition instead of triazepine formation.

Experimental

2,4-Dimethoxy-2′-phthalimidobenzophenone.—Phthaloylanthranilic acid (10 g.) and phosphorus pentachloride (8 g.) were refluxed in dry carbon disulphide (50 ml.) until evolution of hydrogen chloride ceased (2½ hr.). Dimethylresorcinol (6 g.) was added to the cooled solution, and then anhydrous aluminium chloride (12·5 g.) in small portions during 30 min.; a dark red precipitate was formed. After refluxing (1½ hr.), the carbon disulphide was decanted and the complex decomposed with hydrochloric acid and ice. The product was washed with dilute hydrochloric acid, then with water, and finally with a little ethanol which removed most of the impurities. The residue was treated with charcoal in acetic acid, and recrystallised from dilute acetic acid, to yield *2,4-dimethoxy-2′-phthalimidobenzophenone* (8 g., 55%) as colourless rods, m. p. 231—232° (Found: C, 71·6; H, 4·4; OMe, 15·6. $C_{23}H_{17}O_5N$ requires C, 71·3; H, 4·4; OMe, 16·0%). The compound is soluble in glacial acetic acid, acetone, benzene, and hot ethanol, only slightly in cold ethanol, and insoluble in water and ether.

5-(2,4-Dimethoxyphenyl)-12-oxobenzo[5,6]-1,2,4-triazepino[3,4-a]isoindole (IIa).—2,4-Dimethoxy-2′-phthalimidobenzophenone (2 g.) was suspended in ethanol (40 ml.), aqueous 95% hydrazine (0·3 ml.) added, and the mixture refluxed. After about 30 min. fine white needles crystallised, while the starting material slowly dissolved. Refluxing was continued for 30 min. after no more starting material could be seen (total 4 hr.), then the mixture was cooled and filtered. The *product* melted at 271—272°, this m. p. being unchanged by recrystallisation from chloroform (yield, 1·9 g., 95%) (Found: C, 72·1; H, 4·5; N, 10·7; OMe, 15·6. $C_{23}H_{17}O_2N_3$ requires C, 72·1; H, 4·4; N, 11·0; OMe, 16·2%); $\lambda_{max.}$ were at 342, 328, 305, 283, and 230 mμ (log ε 4·13, 4·14, 4·15, 4·48, and 4·56); $\nu_{max.}$ (in Nujol) were at 1712 vs, 1612, 1579, 1552, 1514, 1490, and 1473 cm.$^{-1}$. The compound is insoluble in water, alkali, mineral acid, ether, ethanol, and most organic solvents, but soluble in hot chloroform, pyridine, the higher alcohols, and glacial acetic acid.

2-Phthalimidobenzophenone.—2-Aminobenzophenone (0·7 g.) and phthalic anhydride (0·5 g.) were fused together at 180—200°. The cooled melt was extracted with ethanol (charcoal), and on dilution crystallised. Recrystallisation from dilute ethanol yielded *2-phthalimidobenzophenone*, m. p. 198—199° (Found: C, 76·9; H, 3·9; N, 4·3. $C_{21}H_{13}O_3N$ requires C, 77·1; H, 4·0; N, 4·3%).

Reaction with Hydrazine.—2-Phthalimidobenzophenone (0·3 g.) was refluxed with aqueous 95% hydrazine (4 drops) in ethanol (10 ml.). The solution became yellow and crystals were precipitated within a few minutes. After refluxing (4 hr.) the solution was cooled; the crystals were filtered off and recrystallised from ethanol to yield phthalhydrazide, m. p. 333—334°. The alcoholic solution was evaporated, the residue taken up in ether, and the ether solution evaporated to dryness; the residue obtained on recrystallisation from dilute ethanol yielded 2-aminobenzophenone (0·17 g., 94%), m. p. and mixed m. p. 103—105°.

2,4-Dimethoxy-β-phthaloylpropiophenone.—β-Phthalimidopropionic acid (10 g.) and phosphorus pentachloride (9·5 g.) were refluxed in dry carbon disulphide (50 ml.) for 1½ hr. To the cooled solution was added dimethylresorcinol (7 g.), and then powdered aluminium chloride (16 g.) was added during 30 min. The whole was refluxed for 1½ hr. The purple sticky solid complex was decomposed with ice and hydrochloric acid, and the excess of dimethylresorcinol and carbon disulphide were removed in steam. The solid residue was washed with aqueous sodium hydrogen carbonate, and recrystallised from ethanol, to yield *2,4-dimethoxy-β-phthalimidopropiophenone* (7 g., 52%) as needles, m. p. 151—152° (Found: C, 66·9; H, 5·2. $C_{19}H_{17}O_5N$ requires C, 67·2; H, 5·0%), soluble in most organic solvents but insoluble in water, acids, and alkalis.

Refluxing this compound in alcoholic suspension with hydrazine gave phthalhydrazide within a short time.

Reaction of Hydrazine with 2-Benzamido-5-methylbenzophenone.—2-Benzamido-5-methylbenzophenone (0·6 g.) was refluxed with 95% aqueous hydrazine (1 equiv.) in ethanol (40 ml.)

for 6 hr. Nothing separated and on evaporation of the pale yellow solution a yellow gum was obtained from which no condensation product could be isolated; only small amounts of an acid-soluble substance, which could not be purified, were isolated.

4-*Methoxy*-2′-*phthalimidobenzophenone*.—*o*-Phthalimidobenzoic acid (10 g.) was refluxed with phosphorus pentachloride (8 g.) in anhydrous *sym*-tetrachloroethane (100 ml.) until evolution of hydrogen chloride had practically ceased (1½ hr.). After cooling, dry anisole (4·6 g.) was added and then aluminium chloride (13 g.) during 30 min. A deep purple solution was produced in a marked exothermic reaction. The mixture was heated at 40—50° for 1½ hr. and left at room temperature for a further 1½ hr. before decomposition with ice and hydrochloric acid. Solvent and unchanged anisole were removed by steam-distillation, and the crude solid residue was recrystallised (charcoal) from dilute acetic acid, to yield 4-*methoxy*-2′-*phthalimidobenzophenone* as fine needles (10·2 g., 76%), m. p. 206—207° (Found: C, 73·6; H, 4·3; N, 3·9. $C_{22}H_{15}O_4N$ requires C, 73·9; H, 4·2; N, 3·9%). Condensation in carbon disulphide gave only a 32% yield.

5-p-*Methoxyphenyl*-12-*oxobenzo*[5,6]-1,2,4-*triazepino*[3,4-a]*isoindole* (IIb).—4-Methoxy-2′-phthalimidobenzophenone (1 g.) was suspended in ethanol (40 ml.), aqueous 95% hydrazine (0·15 ml.) added, and the mixture refluxed, with two further additions of hydrazine (0·05 ml. each) at hourly intervals. Within 1 hr. all starting material was dissolved; then needles soon separated. After 4 hours' refluxing, the solution was cooled and filtered, and the needles were washed with ethanol to give the *product*, (0·9 g., 91%), m. p. 241—242°. Recrystallisation from glacial acetic acid did not change the m. p. (Found: C, 74·4; H, 4·25; N, 11·7. $C_{22}H_{15}O_2N_3$ requires C, 74·8; H, 4·25; N, 11·9%). $\lambda_{max.}$ were at 347, 306, 291, and 233 mμ (log ε 4·13, 4·38, 4·45, and 4·55), and $\nu_{max.}$ (in Nujol) at 1712 vs 1612, 1579, 1550, 1519, 1488, 1470 cm.$^{-1}$.

Reduction of 2-*Amino*-4′-*methoxybenzophenone*.—(a) *Catalytic*. In presence of Adams catalyst (0·3 g.) in ethanol (100 ml.) 2-amino-4′-methoxybenzophenone (2·9 g.) absorbed 1 mol. of hydrogen under 3 atm. in 20 hr. After filtration, the filtrate was evaporated to give a yellow oil. Formed in, and recrystallised from, ethanol o-*aminophenyl*-p-*methoxyphenylmethanol picrate* had m. p. 151·5—153·5° (Found: C, 52·8; H, 3·5; N, 12·4. $C_{20}H_{18}O_9N_4$ requires C, 52·4; H, 4·0; N, 12·4%).

(b) *With sodium in ethanol*. 2-Amino-4′-methoxybenzophenone (5 g.), in ethanol (50 ml.), was added rapidly to sodium wire (5 g.). The vigorous reaction was allowed to proceed unchecked. Later, more hot ethanol (20 ml.) was added and the mixture warmed till the sodium had dissolved. The hot solution was diluted with water (250 ml.), and the alcohol removed by steam-distillation. The remaining solution was extracted with ether, the ether evaporated, and the solid residue taken up in benzene (10 ml.). Concentrated hydrochloric acid (10 ml.) was added to this solution and, on chilling in ice, the solid hydrochloride of the amine separated. It was washed with benzene, dried, and dissolved in hot water. This solution was made alkaline with ammonia and extracted with ether. Evaporation yielded an oil (3·5 g.) which solidified. Recrystallising a small amount from light petroleum yielded 2-amino-4′-methoxydiphenylmethane as needles, m. p. 52—55°. The crude amine (1 g.) was fused with phthalic anhydride (0·7 g.) at 180—200° for 20 min. Recrystallising the solid obtained on cooling from dilute ethanol yielded 4-*methoxy*-2′-*phthalimidodiphenylmethane* (1 g., 62%) as plates, m. p. 142—145° (Found: C, 76·7; H, 5·0; N, 3·95. $C_{22}H_{17}O_3N$ requires C, 76·9; H, 3·0; N, 4·1).

Refluxing this phthalimido-compound with hydrazine in ethanol yielded phthalhydrazide and the free amine.

2,4-*Dimethoxy*-3′-*phthalimidobenzophenone*.—*m*-Phthalimidobenzoic acid (10 g.), phosphorus pentachloride (8 g.), and anhydrous *sym*-tetrachloroethane (75 ml.) were refluxed together till evolution of hydrogen chloride ceased (1 hr.). To the cooled solution was added dimethylresorcinol (6 g.), then aluminium chloride (12·5 g.) during 30 min. When the reaction subsided, the mixture was heated at 50° for 1 hr. and decomposed with ice and hydrochloric acid. The solid obtained, after removal of the solvent and excess of dimethylresorcinol in steam, was recrystallised (charcoal) from acetic acid, to yield 2,4-*dimethoxy*-3′-*phthalimidobenzophenone* (9 g., 62%) as needles with a pale iridescent emerald colour, m. p. 166—168° (Found: C, 70·9; H, 4·5; N, 3·5. $C_{23}H_{17}O_5N$ requires C, 71·3; H, 4·4; N, 3·6%).

This benzophenone (2 g.) was refluxed with ethanol (40 ml.) and 95% hydrazine solution (0·5 ml.). The solution became yellow immediately and after 30 min. phthalhydrazide (identified by m. p. and mixed m. p.) separated.

p-*Phthalimidobenzoic Acid.*—*p*-Aminobenzoic acid (10 g.) and phthalic anhydride (10·8 g.) were refluxed in glacial acetic acid (120 ml.) for 1 hr. The mixture was poured into excess of water, and the solid filtered off, washed with water, and recrystallised from 96% ethanol to give p-*phthalimidobenzoic acid* (15 g., 77%) as needles, m. p. 285—287° (Found: C, 67·2; H, 3·3; N, 5·1. $C_{15}H_9O_4N$ requires C, 67·4; H, 3·4; N, 5·2%).

2,4-*Dimethoxy*-4′-*phthalimidobenzophenone.*—Starting with *p*-phthalimidobenzoic acid (10 g.), using the same reagents and procedure as for the 3-phthalimidobenzophenone, and recrystallisation from acetic acid yielded 2,4-*dimethoxy*-4′-*phthalimidobenzophenone* (9 g., 62%) as needles with a pale emerald colour, m. p. 185—187° (Found: C, 70·8; H, 4·6; N, 3·5. $C_{23}H_{17}O_5N$ requires C, 71·3; H, 4·4; N, 3·6%).

When the benzophenone (2 g.) and 95% aqueous hydrazine (0·5 ml.) in ethanol (40 ml.) were refluxed, phthalhydrazide (identified by m. p. and mixed m. p.) was precipitated in 30 min.

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