nitrous oxide. From the experiments on cats there can be little doubt that all the volatile anaesthetics tested increase the excitability of the pulmonary stretch-receptors, and that this increased excitability is largely responsible for the reduction in the depth of respiration. Thus, shallow breathing may be produced by all these anaesthetics alike, the difference between them being only one of degree.

On the other hand, the rate of respiration is affected differently by the anaesthetics tested. Evidence has been obtained in rabbits that those deflation-reflexes which produce acceleration of breathing, are briefly stimulated but then paralyzed by ether, whereas they are stimulated throughout exposure to trichlorethylene. The increased rate of respiration during administration of trichlorethylene is therefore probably due to the cutting short of expiration as well as of inspiration.

As the normal pattern of respiration is determined by the co-ordinated activity of both the stretch-reflexes and the deflation-reflexes, the sensitization of both is believed to account for the clinically familiar disturbances of respiration during anaesthesia, and in particular for the rapid and shallow breathing which is so conspicuous with trichlorethylene.

The work described here has been the subject of a fuller report elsewhere (*J. Pharmacol.*, 1944, **81**, 340-359).

THE SEARCH FOR MORPHINE SUBSTITUTES

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Until the 19th century, the remedies used in medical practice were either inorganic mineral salts or crude extracts from plants. As the study of organic chemistry progressed, these crude extracts were analyzed, their active constituents were isolated and their constitution determined. From this the next step was to try to synthesize these substances in the laboratory from such materials as coal tar, etc., and a further step was taken when attempts were made to improve on nature by altering the formula of a substance slightly and so enhancing its therapeutic effects.

Some Early Synthetic Remedies

A very good example of the progressive steps leading to the discovery of a new remedy is the work which led to the introduction of aspirin. The willow-bark, or *Salix alba*, was known to the ancients as an antipyretic. In 1827, Leroux extracted from willow-bark the bitter glycoside called salicin. From salicin Piria in 1838 made salicylic acid. In 1844, Cahours made the same salicylic acid from oil of wintergreen. This marks the end of the first stage, the isolation of the active principle from the natural source.

The next stage was accomplished by Kolbe and Lautemann, who in 1860 prepared salicylic acid from phenol. However, salicylic acid itself has only a limited therapeutic use owing to its irritant qualities, so the next stage was to try to modify the molecule in such a way as to enhance the good effects and diminish the bad. This was accomplished when Dreser introduced aspirin, or acetylsalicylic acid, in 1899.

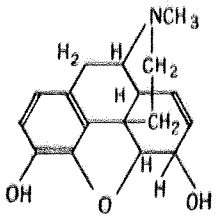
The earliest record of the production of an entirely synthetic remedy was the synthesis of chloral by Liebig in 1832. He produced this by the chlorination of absolute alcohol, which is the method used to-day. Chloral hydrate, produced by the cautious addition of water to chloral, was introduced into medicine as a hypnotic by Liebreich in 1869. Liebreich thought that chloral hydrate would be broken down to chloroform in the body, but in this of course he was wrong.

Other achievements along the same lines were the synthesis from coal tar of acetanilid by Cahn & Hepp in 1886, and later of phenacetin, and the introduction of barbitone by Fischer & von Mering in 1903.

The Opium Alkaloids

Opium, which has been used in medicine for centuries, is now known to consist of a mixture of alkaloids which are the active principles, and of other substances which have no therapeutic value. Up till the end of the 18th century only crude extracts of opium were available, but in 1816 Sertürner described the isolation of the most potent of the opium alkaloids, morphine (Fig. 1). Subsequently 5 other

FIG. 1. MORPHINE



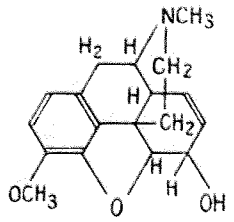
alkaloids were isolated, namely codeine, thebaine, papaverine, and narceine. Narcotine had previously been isolated by Derosne. The three alkaloids responsible for the analgesic properties of opium—morphine, codeine and thebaine—are built up on the phenanthrene-ring system. As these compounds are related in chemical structure, so are they in biological activity, the differences between them being in the degree, rather than in the nature, of their activity. Thus the analgesic, respiratory-depressant, convulsant, emetic and other effects of morphine are all reproduced in codeine, but in codeine the analgesic and depressant effects are weaker and the convulsant effects stronger.

One very undesirable property shared by all the phenanthrene alkaloids of opium is the liability to cause addiction. Drug addiction became such a serious problem in the United States that a special committee was set up to try to find synthetic analogues for morphine which would reproduce the analgesic properties without the undesirable side-effects. Since there appeared to be a definite relationship between chemical structure and biological activity, it was thought that the best way to tackle the problem would be to try to find out if possible what parts of the morphine molecule are specific for its different effects.

New Compounds Prepared by Substitution

The first approach made was to try the effect of substitutions in the groups attached to the phenanthrene nucleus, and in particular the phenolic and alcoholic OH groups. Comparing morphine with the other alkaloids in this series, it is seen that the masking or replacement of these groups makes a considerable difference to the pharmacological action. Codeine (Fig. 2), for instance, in which the phenolic,

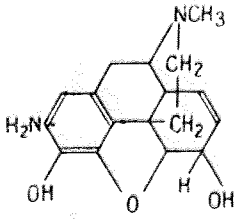
FIG. 2. CODEINE



OH is replaced by OCH_3, is much more convulsant and much less analgesic and narcotic than morphine. A large number of compounds was made and, on the whole, it was found that substitutions in the alcoholic OH group enhanced the analgesic effects. Unfortunately, however, as the analgesic effects were enhanced, the toxicity and convulsant effects were increased too, so that these compounds were of no practical value.

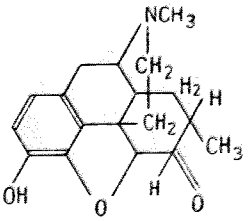
A further method that was tried was that of nuclear substitution, for instance the introduction of a basic amino group at carbon -2 (2-aminomorphine) (Fig. 3). This caused

FIG. 3. 2-AMINOMORPHINE



a decrease in the morphine-like properties. However, one substance produced along these lines, methyl dihydromorphinone (Fig. 4), has been found to be of therapeutic value, as it is twice as effective in analgesic action and its duration of action is as long as that of morphine. In the cases in which it was tried, no emetic or respiratory depressant action was observed.

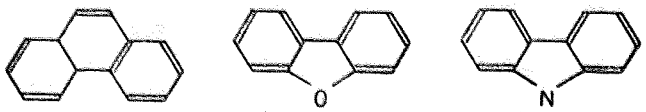
FIG. 4. METHYL DIHYDROMORPHINONE



Building on the Phenanthrene or Similar Nuclei

Yet another method was to start, not from the morphine molecule itself, but from the simple phenanthrene nucleus, or from some other nucleus, such as dibenzofuran or carbazol. The general formulae of these are shown in Fig. 5. The most

FIG. 5



effective analgesic among the derivatives from the phenanthrene nucleus was 3-py-tetrahydroiso-quinolino-4-hydroxy-1,2,3,4-tetrahydrophenanthrene. The carbazol derivatives appeared to be the most promising of all the synthetic substances, with high analgesic and narcotic effects, low toxicity and little emetic action. The most active member of this series was 9-methyl-2(1-hydroxy-3-diethyl amino) propyl carbazol. Of the substances submitted to clinical trial the most promising was methyl dihydromorphinone.

Synthetic Analogues

Another group of workers (Dodds, Lawson & Williams, 1944) approached the problem from a rather different angle. Bearing in mind that stilboestrol, which bears only loose chemical relationship to the naturally-occurring oestrogens, is able to replace these in every way, these workers considered the possibility that synthetic analogues might be found for other naturally-occurring substances containing the phenanthrene ring system.

As a starting point diphenylethylamine was tested, and then 17 derivatives of this were prepared and investigated. Their code-numbers, chemical names and formulae are given in Fig. 6.

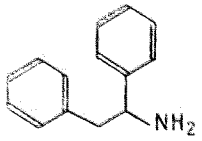
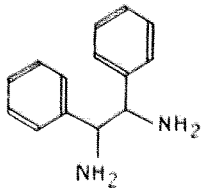
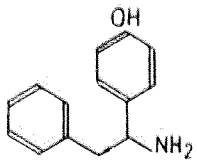
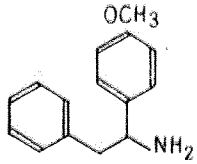
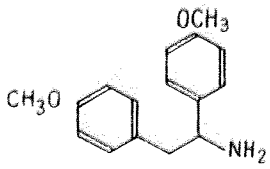
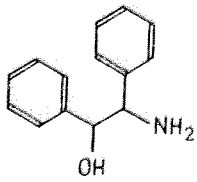
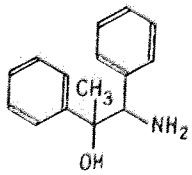
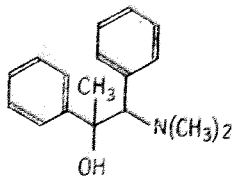
Animal Tests : The criteria of the biological tests were depression of the righting-reflex in rats, rise in the blood-sugar in rabbits, and the effects of intramuscular injections in cats. Five of the compounds were tested clinically.

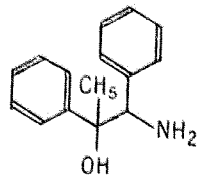
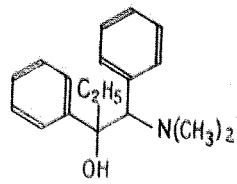
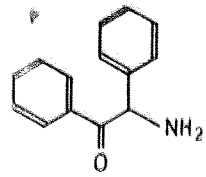
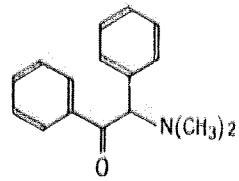
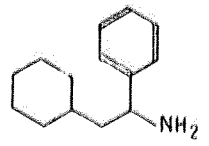
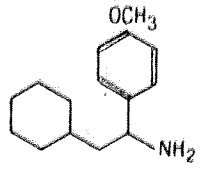
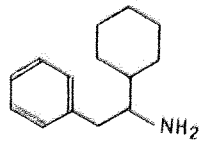
The synthetic compounds were all found to have less capacity than morphine for depressing the righting-reflex in rats. There did not appear to be any coherent relationship between chemical structure and pharmacological activity. It was found that the di-amino compound (M2) appeared to have no depressant activity at all. The β-hydroxy compound (M4) and the compounds with hydroxy or methoxy groups attached to one or both phenyl rings (M15, M14, and M1) were less active than the parent compound (M3). On the other hand, the cyclo-hexyl compounds (M16 to M18) were more active, but more toxic, than the parent compound.

With regard to the effects on the blood-sugar of rabbits, diphenylethylamine was found to have a marked capacity for raising the blood-sugar, although the doses required were larger than the doses of morphine required. Addition of an amino group in the β-position was found to increase the activity (M2,) as also the addition of a single hydroxy group to the α-phenyl ring (M15), but methylation of this phenolic hydroxy group (M14) markedly increased the activity. The cyclo-hexyl compounds (M16 to M18) appeared to be the most active of all.

The effects of the compounds on cats were difficult to assess, as the number of animals available was very small and cats vary very much in their individual response to the

FIG. 6. DIPHENYLETHYLAMINE AND RELATED COMPOUNDS

Code No.	Chemical Name	Formula
M3	$\alpha\beta$-diphenylethylamine	
M2	$\alpha\beta$-diphenyl-ethylene-diamine	
M15	α-(p-hydroxyphenyl)-β-phenyl ethylamine	
M14	α-(p-anisyl)-β-phenyl ethylamine	
M1	4 : 4′-dimethoxy-$\alpha\beta$-diphenylethylamine	
M4	β-hydroxy-$\alpha\beta$-diphenyl ethylamine	
M5	β-hydroxy-$\alpha\beta$-diphenyl-n-propylamine	
M8	β-hydroxy-$\alpha\beta$-diphenyl-n-propyl dimethylamine	

Code No.	Chemical Name	Formula
M6	β-hydroxy-$\alpha\beta$-diphenyl-n-butylamine	
M9	β-hydroxy-$\alpha\beta$-diphenyl-n-butyl dimethylamine	
M12	α-amino-deoxy benzoin	
M7	dimethylamino-benzyl-phenyl-ketone	
M16	α-phenyl-β-cyclo-hexyl ethylamine	
M17	α-(p-anisyl)-β-cyclo-hexyl ethylamine	
M18	α-cyclo-hexyl-β-phenyl-ethylamine	

effects of morphine. Diphenylethylamine and its β-hydroxy derivative (M4) both produced pupil dilatation and hyper-excitability in cats. Addition of methyl or ethyl groups also in the β-position (as in M5 or M6) appeared to increase the activity, and it was still further increased by methylation of the amino nitrogen (as in M8 and M9). Three of the compounds (M7, M16 and M18) produced vomiting, and others produced nausea, licking of the lips, and salivation.

Clinical Tests : Five of the compounds, M3, M4, M2, M7, and M18, were tested clinically. For this purpose they were administered orally to patients suffering from pain due to malignant disease and who were having morphine at 4-hourly intervals. The substances to be tested were substituted for

the morphine without informing the patient. Substances M2, M7 and M18 were found to be inactive. M3, when given in doses of 200 mg. every 3 hours, was found to relieve the pain, but mental confusion developed after about one hour. When given to normal persons, M3 produced elation and slight muscular incoördination. M4 was tried on 14 patients and gave complete relief of pain in all cases without any signs of mental confusion or undesirable after-effects.

Extensive clinical investigation, however, showed that this series of compounds relieved only pain associated with nerve-pressure. They were found to be completely effective in cases of carcinomatous growth pressing on nerves, but appeared to be without any activity on pain caused by inflammatory processes and similar conditions. It must, of course, also be emphasized that substances of this series at present investigated are of only theoretical interest, and are not suitable for adoption into clinical practice. It may well be, however, that further investigations in this series would succeed in producing substances of actual clinical importance.

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819

SYNTHETIC SUBSTITUTES FOR ATROPINE

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During the war need arose to investigate synthetic mydriatics which might be used in place of atropine if supplies of the latter became inadequate. Synthetic atropine was thought to present a far too difficult manufacturing problem and the only synthetic mydriatic of the atropine type in common use, viz. eucatropine, is a much less powerful drug. The supply of homatropine is, of course, dependent upon the same sources as atropine.

Atropine is an ester of an amino-alcohol (tropine) and a phenylhydroxypropionic acid (tropic acid). Jowett & Pyman (1910) had shown that synthetic esters of tropine display marked mydriatic activity on local application to the eye only when the esterifying acid contains both a phenyl and a hydroxyl group. Braun, Braunsdorf & Räth (1922), Fromherz (1933) and other workers had also shown that the tropine part of the molecule could be replaced by simpler and more readily accessible amino-alcohols without complete loss of mydriatic activity. The problem resolved itself into finding the optimal combination of amino-alcohol and acid.

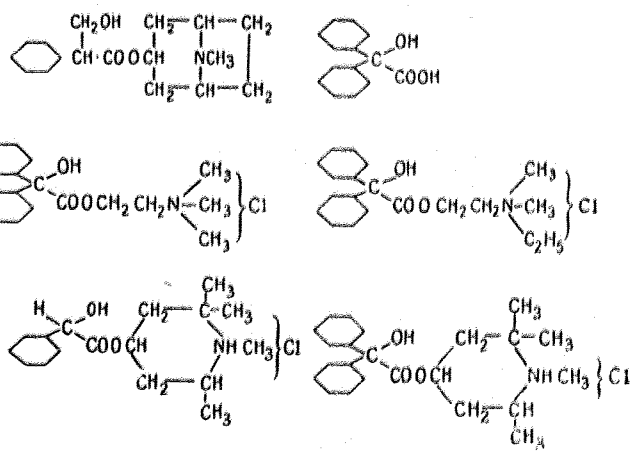
The work of Blicke and his collaborators (Blicke & Maxwell, 1942; Blicke & Kaplan, 1943) suggested that benzilic acid was the most suitable acid; it contains two phenyl groups and a hydroxyl, and consequently fulfils the conditions laid down by Jowett & Pyman. Unfortunately Blicke made no quantitative comparison of his compounds with atropine, and it is therefore difficult to judge the relative merits of the different amino-alcohols which he used; moreover, several of his mydriatic benzilic esters were also described as excellent local anaesthetics, a result which throws doubt on the truly atropine-like character of their mydriatic action.

The mydriatic effect of atropine is the result of an antagonism to acetylcholine and it was thought that the same effect might be achieved by a suitable choline ester; for this reason the benzilic and tropic esters of choline were first prepared. Benzilylcholine chloride had about 30% of the mydriatic effect of atropine (in mice) and tropylcholine chloride about 15%. These results led to a systematic study of benzilic esters of the general formula:

$$(C_6H_5)_2C(OH).COO(CH_2)_nNR\,R'\,R''\}X,$$

where R, R′ and R″ are alkyl groups, X is a halide anion, and n = 2 or 3. Before discussing the results of this study, it may be well to outline briefly the method used to estimate mydriatic activity.

FIG. 1. FORMULAE OF ATROPINE AND SYNTHETIC SUBSTITUTES INVESTIGATED



Methods

All the early work on synthetic mydriatics involved a comparison of the effects produced by the instillation of standard solutions of atropine and of the synthetic substances into the eyes of cats or rabbits; this method allows only a qualitative judgment of relative activity. A quantitative method was described by Pulewka (1932) in which the drug is injected into mice and the diameter of the pupil is measured directly by means of a binocular microscope with a scale in the eyepiece.

Groups of mice, of approximately uniform weight (15-20 g.), are injected intraperitoneally with 0·2 ml. of the solution to be tested and the size of the pupil is measured in the arbitrary units of the eyepiece scale. The effect of atropine reaches its maximum in 15 minutes and begins to decline after 25 minutes; for this reason, readings of pupil-diameters are made between 15 and 20 minutes after the injection.

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